Studies of Dysmorphogenesis in Children with Oral Clefts: 1. Relationship between Clinical Findings and School Performance

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In children with oral clefts, the risk of additional abnormalities is increased (*1*). These may take the form of minor developmental deviations (variant morphogenesis), a second major malformation, or neurologic dysfunction. Impaired school performance is also a problem in a significant proportion of children with oral clefts (*2, 3*). In many cases the school difficulties can be related to specific handicaps (such as speech or hearing problems or emotional disturbance) that may be secondary to the oral cleft, or to the handicap imposed by a second major malformation or a neurologic abnormality. In other cases, however, no specific handicapping condition is evident to account for school difficulties.

A clinical impression had been gained that school difficulties were more prevalent in the children who exhibited additional minor dysmorphogenetic features than in those who lacked such features; but it was not clear whether the apparent association was the result of an increased prevalence of specific school-handicapping conditions in the children with such features. In an effort to clarify the relationship between clinical abnormalities, specific handicapping conditions, and school performance, a series of children with oral clefts were studied.

The reasoning behind the specific hypothesis to be tested in this study was as follows: Oral clefting is a signal of a disturbed course of embryonic development. If the disturbance is localized, there should be no morpho-

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logic abnormalities outside the area of the cleft, and brain development should be generally normal.

On the other hand, if the oral cleft is but one manifestation of a more diffuse disturbance of embryonic growth and differentiation (a disturbance which might be either *regional*, involving the craniofacial structures, or *general*, involving the entire body), then there should be additional minor and/or major dysmorphogenetic features, and in some such children, brain development might be impaired. Subsequent school performance in such children might therefore reflect not only the problems and handicaps associated with clefting, but also the additional factor of developmental deficit.

This line of reasoning thus led to the hypothesis as finally formulated: Among children with oral clefts, the presence of additional minor/major dysmorphogenetic features will be associated with increased risk of impaired school performance or frank mental deficit. The association will persist even after removal from the study of children with detectable school-handicapping conditions.

Methods

A. Ascertainment. The children were ascertained through attendance at the Cleft Palate Clinic of the University of Michigan during a 2-year period (1969–71). Although they do not constitute a random sample of children with oral clefts, they are probably reasonably typical of children referred to a large university cleft palate center. Specifically, they were not selected because of school difficulties or physical features other than the oral cleft. Each child was evaluated by a team composed of an oral surgeon, plastic surgeon, orthodontist, pedodontist, otolaryngologist, speech pathologist, speech therapist, audiologist, and pediatrician. Where special problems were detected, additional specialists were consulted; e.g., pediatric cardiologist, psychologist, psychiatrist.

B. Classification by Attributes. Oral clefts were classified as isolated cleft palate (CP) or cleft lip with or without cleft palate (CL(P)). This classification is in accord with studies suggesting systematic etiologic differences in the two groups (*4*).

Clinical features studied include major malformations (in addition to the oral cleft), and minor dysmorphogenetic features (such as hypertelorism, clinodactyly, etc.).

For the purpose of the present study, minor dysmorphogenetic features were scored on a 3-level scale (0, 1, and 2 or more features). Features occurring in the oronasal area, that could be considered as part of the disturbance producing the cleft itself, were not included.

In addition, certain conditions (such as deafness, speech difficulty, neurologic abnormalities, etc.) that could constitute handicaps to good school performance were recorded. A child assigned to a speech therapy class was

considered speech-handicapped, even though the speech difficulty might be minimal. Similarly, all but the mildest hearing loss (<20 dB) was considered a handicap. The purpose was to ensure that the group defined as "not handicapped" would be relatively free of detectable conditions that could affect school performance.

Since detailed psychometric test results were available for only a few of the children studied, no attempt was made in this preliminary study to assess "intrinsic" intellectual ability. Instead, objective school performance was recorded on a 3-level scale: Level I: doing well (A's, B's, some C's) in regular school classes; Level II: doing poorly in school (C's, D's, failure in one or more subjects; held back a year); Level III: in special education class or not intellectually able to attend school. Information regarding school performance was obtained directly from a parent or guardian.

Results

Complete data were available for 101 school-age children (65 boys, 36 girls). All but 4 were Caucasian. Data are summarized in Table 1. The overall prevalences of the attributes studied obviously cannot be safely extrapolated outside the clinic situation, but the focus of this study is on the associations of the various attributes.

A. Variant Morphogenetic Features. Almost ¾ of the children (74 out of 101) exhibited one or more minor dysmorphogenetic features (Tables 1 & 2) and of these, 48, or nearly half the total, exhibited two or more such features. Dysmorphogenetic features tended to cluster in individuals, a finding in accord with previously reported observations in children with a major malformation (*5, 6*). The proportion of children with multiple minor features was highest in boys with isolated cleft palate (16 out of 23 (70%)) and lowest in girls with cleft lip-palate (5 out of 18 (28%)) (chi-square = 5.5, p less than 0.025).

B. Major Malformations. Major malformations are tabulated in Table 3, together with the judgment as to whether the malformation could reasonably be considered as a possible handicap to good school performance. Interestingly, there was a strong tendency for the *second* major malformation (i.e., in addition to the oral cleft) to occur in children with multiple additional minor dysmorphogenetic features, lending support to the belief that the distinction between major and minor malformations is somewhat arbitrary.

C. Neurologic Dysfunction. Signs of neurologic abnormality occurred in 15 children (11 boys, 4 girls) (Table 4). All were classed as potentially handicapping with respect to school performance.

D. School-Handicapping Conditions. These are listed in Table 5. (Note that the list includes all neurologic abnormalities as well as certain of the major malformations). School-handicapping conditions did not tend, in this series, to cluster in individuals.

TABLE 1A and 1B. Distribution of Children with Oral Clefts by School Performance Level (1, 11, or 111); Degree of Dysmorphogenesis (D_0, D_1, D_2: zero, one and two or more Dysmorphogenetic features, respectively); and presence or absence of Handicap (H). Note increased risk of impaired school performance (Level 11 or 111) associated with presence of Handicap and of additional dysmorphogenetic features.

A. *Cleft palate*

D	*H*	*level*			*sum*
		I	*II*	*III*	
0	−	5	0	1	6
	+	1	0	0	1
	sum	6	0	1	7
1	−	3	2	0	5
	+	1	1	2	4
	sum	4	3	2	9
2	−	2	2	3	7
	+	7	7	4	18
	sum	9	9	7	25
sum	−	10	4	4	18
	+	9	8	6	23
	sum	19	12	10	41

B. *Cleft lip-palate*

D	*H*	*level*			*sum*
		I	*II*	*III*	
0	−	13	1	0	14
	+	5	1	0	6
	sum	18	2	0	20
1	−	10	4	0	14
	+	0	3	0	3
	sum	10	7	0	17
2	−	4	1	0	5
	+	12	3	3	18
	sum	16	4	3	23
sum	−	27	6	0	33
	+	17	7	3	27
	sum	44	13	3	60

TABLE 2. Minor dysmorphogenetic features observed in 5 or more individuals in this series. Ear anomalies and various types of clinodactyly have been combined.

most frequently observed dysmorphogenetic features	
1. epicanthal folds	25
2. tilted palpebral fissures	20
antimongoloid	14
mongoloid	6
3. prominent/malformed ears	10
4. short great toe	8
5. hypertelorism	7
6. generalized skeletal dysplasia	7
7. undescended testis	7
8. clinodactyly (any type)	6
9. brachycephaly	5
10. small or malformed thoracic cage	5
11. short fifth finger	5

E. Relationship of Handicaps and Variant Morphologic Features to School Performance. Table 1 demonstrates the most striking finding of this study, namely, that children with additional dysmorphogenetic features (in addition to the oral cleft) are also at increased risk of impaired school performance (chi-squared with 4 degrees of freedom = 12.4; p less than 0.01). Of 27 children lacking dysmorphogenetic features, only 3 were doing poorly in school, whereas almost half (35 out of 74) of the children with such features were doing poorly in school (chi-squared with one degree of freedom = 9.5; p less than 0.002). Of 13 frankly retarded children (Level III), only one was free of minor dysmorphogenetic features.

TABLE 3. Major malformations occurring in 22 out 101 children with oral clefts.

H: judged to represent a significant potential handicap to good school performance.

$\overline{H}$: judged not to represent a school handicap.

*: repaired in infancy or early childhood.

†: systolic murmurs judged to represent small ventricular septal defect.

‡: no symptoms or signs; not further diagnosed.

major malformations	$\overline{H}$	*H*	*total*
1. inguinal hernia	6*	0	6
2. congenital heart disease	2†	3*	5
3. significant heart murmur	5‡	0	5
4. malformed hands	0	5	5
5. vertebral anomalies	2	0	2
6. imperforate anus	1*	0	1
7. myelomeningocele	0	1*	1
8. encephalomyelomeningocele	0	1*	1
	16	10	26

TABLE 4. Neurological abnormalities (observed or reported) occurring in 15 out of 101 children with oral clefts.

neurological abnormalities	
A. major findings	
grand mal seizures (by history)	3
minor motor seizures (questionable)	1
spasticity	3
ataxia	1
athetosis	1
tremor, essential	1
sensorineural hearing loss	2
B. minor findings	
hyperactivity	4
mirror writing (by history)	3
short attention span	1
poor visual-motor integration	1
clumsiness	2
	23

By hypothesis, a portion of the impaired school performance in the children with minor dysmorphogenetic features should be attributable to the effect of the additional school-handicapping conditions also noted. Such conditions are in fact more prevalent in the children with multiple dysmorphogenetic features. However, a closer look at the data yields some unexpected findings:

1. For children with no, or only one, dysmorphogenetic feature, the proportion with impaired school performance is higher in the "handicapped" group (7 out of 14) than in the "nonhandicapped" group (8 out

TABLE 5. Conditions judged to be actually or potentially school-handicapping, occurring in 50 of 101 children with oral clefts.

conditions judged to be actually or potentially school-handicapping	
A. communicative	
speech difficulty	12
conductive hearing loss	15
B. anatomic	
malformed hands	5
congenital heart disease	3
other (neural tube defects)	2
C. neurologic	
sensorineural hearing loss	2
neurologic dysfunction	17
hyperkinetic behavior	4
D. other	
multiple operations or prolonged illness causing significant loss of school time	1
emotional disturbance	3

of 39). (By Fisher's Exact Test, the p-value for this comparison is about 0.04). But for children with 2 or more dysmorphogenetic features, there is not even a suggestion of such a trend. Of such children with handicapping conditions, 17 out of 36 were doing poorly in school, while of those without handicapping conditions, 6 out of 12 were doing poorly in school, essentially the same proportion.

2. Considering only the 51 children entirely lacking a detectable handicapping condition, only 2 out of 20 without dysmorphogenetic features were in school performance level II or III, while of 31 with such features, 12 were in school performance level II or III ($p = 0.024$ by Fisher's Exact Test).

These two findings suggest that children with dysmorphogenetic features but without obvious school-handicapping conditions may actually be at increased risk of poor school performance in ways not clinically apparent.

It was considered possible that the relationship between dysmorphogenetic features and impaired school performance could be due in part to the presence of a subgroup of children with identifiable syndromes of dysmorphogenesis and mental retardation. However, removal of 21 children with identifiable syndromes or syndrome-like features did not remove the effect, which was still statistically significant (chi-squared = 7.9, p less than 0.0025). Furthermore, removal of CP males, for whom the risk of impaired school performance is especially high (see below) did not remove the effect (chi-squared = 4.2, p less than 0.025).

F. Relationship of Sex and Type of Oral Cleft to School Performance. The risk of impaired school performance was higher in isolated cleft palate (CP) (22 out of 41, or 54%) than in CL(P) (16 out of 60, or 27%) (chi-squared about 6.5, p about 0.01). However, this effect was largely due to the greater risk for males with CP (15 out of 23, or 65%) as opposed to that for males with CL(P) (10 out of 42, or 24%) (chi-squared = 9.1, p less than 0.005). Among females the type of cleft had little association with impaired school performance.

The question arises, whether the increased risk of impaired school performance among males with CP is associated with a higher prevalence of dysmorphogenesis and/or handicapping conditions in that group:

(1) The overall proportion of dysmorphogenesis is higher in males with CP (21 out of 23) than in males with CL(P) (27 out of 42) (chi-squared = 4.3, p less than 0.05), while no such effect is apparent in females.

(2) There was no difference in risk of handicapping conditions by cleft type, either in males or females.

Among males with 2 or more dysmorphogenetic features, the risk of impaired school performance is higher for CP (12 out of 16) than for CL(P) (5 out of 18) (chi-squared = 5.8, p less than 0.025). But for boys with no, or only one, dysmorphogenetic feature, no such association is apparent.

For females, the corresponding figures are too small for meaningful comparison.

For males without a detectable handicap, the risk of school impairment was higher for CP (6 out of 11) than for CL(P) (3 out of 22) (by Fisher's Exact Test, $p = 0.04$). For females, no trend was apparent.

Thus, the data partially support the conclusion that the risk of school impairment is greater for boys with isolated cleft palate, even after correction for the effects of dysmorphogenesis and clinically detectable handicap.

Discussion

A. The finding of increased risk of additional major malformations and other potentially school-handicapping conditions in the group of children with oral clefts and additional minor dysmorphogenetic features is not surprising. Such a finding tends to reemphasize the importance of the dysmorphogenetic process *per se* as a manifestation of some deleterious general disturbance or disturbances of intrauterine growth and development. What is perhaps more surprising is the indication in the present study that the risk of significantly impaired school performance appears to be increased, even in the *absence* of clinically detectable handicapping conditions, in children with additional dysmorphogenetic features.

It could be objected that the morphologically-stigmatized child may be misclassified in school (on the basis of his physical appearance) as mentally dull and then becomes so in a self-fulfilling prophecy situation. Against this argument are the following facts:

(1) all the children in this study had oral clefts, a prominent form of major malformation. If the oral cleft had not already resulted in such a misclassification, it seems unlikely that the addition of minor dysmorphogenetic stigmata such as epicanthal folds or a short fifth finger would influence the teacher to consider such a child as mentally dull. Furthermore, the removal of 21 children with syndrome-like features fails to abolish the effect.

(2) Cleft lip, with or without cleft palate, is a more disfiguring malformation than is isolated cleft palate. Yet, in this series, the highest prevalence of poor school performance, and the highest risk of frank mental retardation, (Level III) were found in boys with isolated cleft palate. This result is contrary to what would be expected on the "labelling" hypothesis.

Although the present study was restricted to children with oral clefts, its implications extend to congenital malformations in general. The findings suggest that a useful distinction may possibly be made between localized and generalized embryonic dysmorphogenetic processes and that the latter, however mediated (through genetic, infectious, or nutritional events) may be more likely to be associated with impaired brain development.

B. It should be stressed that the relationships here reported are statistical only. Many of the children with multiple dysmorphogenetic features were doing well in school. Further, the number of children studied is very small, and a shift of only a few from one category to another could cause the findings here reported to be non-significant. Independent studies involving larger numbers are highly desirable. Finally, school grades and special class assignments fall far short of being good estimators of either general intellectual potential or specific learning-related abilities. The associations documented in this study should therefore not be incautiously generalized.

Conclusions

1. Children with oral clefts may be divided into two groups on the basis of presence or absence of minor dysmorphogenetic features.

2. This distinction is of clinical importance because the group with additional minor dysmorphogenetic features appear to be at increased risk of school-handicapping conditions and of impaired school performance, whereas those children who lack such features seem to have relatively normal scholastic prognosis. The risk is greater for boys than for girls and is greatest for boys with isolated cleft palate.

3. In children with oral clefts, impaired school performance appears to be as closely related to the presence of minor dysmorphogenetic features as to the effect of detectable school-handicapping conditions, suggesting that one underlying basis for the school difficulties may be, like the dysmorphogenetic features themselves, of prenatal origin.

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References

1. Drillien, C. M., Ingram, T. T. S., and Wilkinson, E. M., The Causes and Natural History of Cleft Lip and Palate, E. and S. Livingtone, Edinburgh and London, 1966.
2. Five Year Report (1955–1959), The Cleft Lip and Cleft Palate Research and Treatment Center. The Research Institute, The Hospital for Sick Children, Toronto, Canada.
3. Goodstein, L. D., *J. Speech and Hearing Disorders 4:* 287 (1961).
4. Fraser, F. C., The Genetics of Cleft Lip and Cleft Palate, *Amer. J. of Human Genetics 22:* 336–352 (1970).
5. Smith, D. W., and Bostian, K. E., *J. of Pediatrics 65:* 189 (1964).
6. Hook, E. B., and Petry, J. J., *Nature* (London) *227:* 847–8 (1970).