

CLEFT LIP AND PALATE: SEASONAL INCIDENCE, BIRTH WEIGHT, BIRTH RANK, SEX, SITE, ASSOCIATED MALFORMATIONS AND PARENTAL AGE

A STATISTICAL SURVEY

BY

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Cleft palate, with or without cleft lip, is one of the more common congenital malformations in man. Two recent English surveys have reported a birth incidence of about one in 600 (MacMahon and McKeown, 1953; Pleydell, 1960) and this conforms well to careful surveys carried out in other countries of Europe (Fogh-Andersen, 1942) and the U.S.A. (Ivy, 1957).

For the past 10 years it has been the practice of the Plastic Surgery Unit at the Churchill Hospital to record in cases of this malformation, information regarding birth weight, date of birth, age of parents and birth rank. The site of the cleft (left, right or central) was always noted and in most cases the presence of any additional congenital malformations. In all, data are available in 456 cases, though the full information is not given in every instance.

The present paper deals with an analysis of these data in an attempt to throw light on possible aetiological mechanisms of this deformity. Group I refers to cases of isolated harelip, Group II to isolated cleft palate and Group III to combined harelip with cleft palate (Davis and Ritchie, 1922).

The Present Inquiry

Edwards (1958a) and Record and Edwards (1958) have detected a strong seasonal trend in the incidence of anencephaly and congenital dislocation of the hip respectively. Thus it seemed worthwhile to analyse the present data, especially as Edwards (1961) has noted a seasonal trend in cases of Group I cleft lip, and our analysis is by the method described in his paper (Table 1). Birth weight, birth rank, sex incidence, site of cleft and associated abnormalities are shown in Tables 2-6.

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The control series for parental age (Table 7) was obtained in the following way. Parental age was recorded in 1,026 consecutive births at University College Hospital from March 1956 to October 1957. A regression was established for father's age on mother's age for each birth rank separately and for the total material. These data could not be used as a control series because of the different age and birth rank distribution of hospital, as opposed to domiciliary, deliveries.

However, using the material in the Registrar-General's report (1954) for maternal age, the expected paternal age could be calculated, using the regressions established as above.

Discussion

The pathogenesis of these malformations is controlled not by any single factor, but by a number of factors both hereditary and environmental, and by interactions between them. Furthermore, the members of a surgical series, as presented here, have only one feature in common—the nature of the lesion to be repaired—and otherwise represent a heterogeneous collection of different entities. Data of this nature cannot differentiate between the roles of heredity and environment in the causation of this condition, still less define clearly any aetiological factors. It can, however, provide pointers in this direction.

Seasonal Incidence. It has been shown by these results (Table 1) that seasonal influences appear to play no significant part in the causation of these malformations. This is in contrast to the findings of Edwards (1961).

Birth Weight. Birth weights are on the whole

TABLE 1
SEASONAL INCIDENCE

Cleft Group	Birth Month												χ^2	Significance		
	1	2	3	4	5	6	7	8	9	10	11	12				
I	4	10	3	11	10	5	10	5	9	7	7	8	1.56	0.5 > p > 0.3		
II	19	14	21	18	19	18	14	11	16	23	9	13			1.91	0.5 > p > 0.3
III	14	6	16	8	17	10	11	16	7	13	16	16				
Total cases ...	37	30	40	37	46	33	35	32	32	43	32	37	0.41	0.9 > p > 0.8		

TABLE 2
BIRTH WEIGHT

Cleft Group	Sex	Totals	Mean Birth Weight of Clefts	S.D.	Mean Birth Weights of Controls	Significance
I	M	53	7.61	0.14	7.61	p > 0.10
	F	26	7.31	0.25	7.31	p > 0.10
II	M	69	7.63	0.15	7.61	0.02 > p > 0.01
	F	83	7.03	0.12	7.31	
III	M	96	7.45	0.14	7.61	p > 0.10
	F	46	7.13	0.20	7.31	p > 0.10

Controls from Birmingham series of McKeown and Gibson (1951) and MacMahon and McKeown (1953) corrected for parity.

TABLE 3
BIRTH RANK

Cleft Group	Position in Family									χ^2	Significance
	1	2	3	4	5	6	7	8	9		
I	35	21	14	8	4	1	0	1	2	0.56	0.5 > p > 0.3
II	74	54	22	7	7	4	3	3	2	0.05	0.9 > p > 0.8
III	51	42	25	14	6	4	1	0	0	0.16	0.7 > p > 0.5
Total cases ...	160	117	61	29	17	9	4	4	4	0.53	0.5 > p > 0.3

The statistical analysis is by the method of Edwards (1958b). The control series is from figures for the whole country published by the Registrar-General for 1954, this being the median birth year of the present series.

low (Table 2). This is not unexpected with a severe congenital malformation and it is interesting that in Group I this decrease is least. It is most marked in Group II females and this conforms to the findings of Lutz (1959).

Birth Rank. The birth rank distribution (Table 3) is not significantly different from normal. However, if it is analysed by the sex of the patient, we find a marked primiparity effect in Group I females.

	Group I (cleft lip only)								
Birth Rank ...	1	2	3	4	5	6	7	8	9
Females ...	16	5	2	4	1	0	0	1	1
Males ...	19	16	12	4	3	1	0	0	1

This effect is not repeated in any other group. (Normal ratio for birth rank 1 to birth rank 2 =

1.32. In Group II males it is 1.25 and in females 1.48, and in Group III males 1.04, females 1.50.)

Incidence, Sex and Site. It has been argued that Groups I and III form one sub-division of this malformation and Group II another. The main argument in favour of this hypothesis has been the similar excess of affected males in Groups I and III (about 2:1 in most series) as opposed to equality or even a slight excess of females in Group II. The present data support this hypothesis (Tables 4 and 5). The possible reasons for the male excess in Groups I and III will be discussed later. The incidence by site conforms well to the data of Fogh-Andersen. No explanation can be given at the moment for the preference of this lesion for the left side. The incidence on the various groups con-

TABLE 4
INCIDENCE AND SEX

Cleft Group	Total	% of Series	Males	Females	Males (%)
I	93	20.4	61	32	65.6
II	211	46.3	94	117	44.5
III	152	33.3	103	49	67.8
Totals ..	456	—	258	198	56.5

TABLE 5
SITE OF CLEFT

Cleft Group	Right	Left	Bilateral
I	27 (29.0%)	48 (51.6%)	18 (19.4%)
II	Central		
III	31 (20.4%)	82 (53.9%)	39 (25.7%)

TABLE 6
ASSOCIATED ABNORMALITIES

Cleft Group	Nos.	Abnormality
I	1	Syndactyly
II	19	Pierre Robin's syndrome (retrognathism)
	4	Klippel Feil's syndrome
	2	Mucous fistulae of lower lip and syndactyly
	1	Treacher Collins' syndrome
	1	Ectrodactyly
	1	Talipes
III	1	Hypospadias
	1	Micrognathia
	1	Polydactyly

forms well to the Birmingham birth data (MacMahon and McKeown 1953), but not to the operative series of Fogh-Andersen who found about 50% of Group

TABLE 7
PARENTAL AGE

Cleft Group	Totals	Father		Mother	
		Mean Age	S.D.	Mean Age	S.D.
I	83	31.4	6.48	28.3	5.81
II	163	32.9	8.43	29.0	5.85
III	136	33.9	7.78	29.3	6.05
Controls		31.6 (var. = 0.14)		28.3	

Comparison with controls:

Group	Significance
I	Fathers $p > 0.1$ Mothers $p > 0.1$
II	Fathers $0.1 > p > 0.05$ Mothers $p > 0.1$
III	Fathers $0.01 > p > 0.002$ Mothers $0.1 > p > 0.05$

III, and roughly equal incidence of Groups I and II. The reason for this discrepancy is not clear.

Associated Malformations. This is an operative and not a birth series. The incidence of congenital malformations (Table 6) would be expected to be lower, therefore, than in the series of MacMahon and McKeown (1953) since all gross malformations would have been excluded by early death. Group II, however, is very interesting from this point of view since isolated cleft palate seems to occur with remarkable frequency as a constituent of syndromes which are inherited in a dominant manner such as those of Pierre Robin and Treacher Collins and ectrodactyly. In addition, a father and son are included with the syndrome of cleft palate with mucous fistulae of the lower lip (Calnan, 1952; Van der Woude, 1954). In our family syndactyly was also present.

The syndrome of Pierre Robin is, however, numerically by far the most important. In the past such children tended to die soon after birth due to the tongue falling back causing asphyxia; they are now surviving with better nursing care, and the condition of the lower jaw improves with age. This syndrome is inherited in an irregularly dominant manner and the gene concerned may account for quite a large proportion of Group II cases. An analysis of parental age was made separately for these complex syndromes and for simple Group II cases, but revealed no differences which could not be attributed to chance.

Parental Age. MacMahon and McKeown (1953) showed that maternal age but not birth rank was raised in Groups I and III but not Group II. We were unable to confirm this for Group I, but found a marked increase in Group III (Table 7). A smaller increase in Group II could well have been due to chance. Furthermore, our data suggest that the more important factor in the raised parental age was the *paternal* and not the maternal age. In an attempt to explain the puzzling asymmetrical distribution of the lesion and the difference in sex incidence an analysis of variance was performed to determine whether this raised paternal age in Group III could be correlated with patients of a particular sex or with a particular site of lesion.

Group III	Males	Females	$\chi^2 = 1.39$ $p = 0.5$
Right	23	8	
Left	43	26	
Bilateral ..	23	13	

Analysis of variance (paternal age) is as follows:

	Degrees of Freedom	Sum of Squares	Mean Square	Significance
Between sexes ..	1	72	72	p>0.2
Between sites ..	2	28	14	p>0.2
Interactions ..	2	41	20.5	
Residual ..	130	8,692	66.86	

This analysis does not show any differences in paternal age by sex or site which are unlikely to be due to chance. However, the age of fathers of female patients is higher than that of males.

Patients	Mean Age of Father	Mean Age of Mother
47 females ..	34.6	29.7
89 males ..	33.1	29.1

Such large differences were not seen in Groups I and II.

Group	Patients	Mean Age of Father	Mean Age of Mother
I	28 females ..	31.5	28.5
	55 males ..	31.0	28.0
II	87 females ..	32.5	28.7
	76 males ..	33.4	29.3

An examination of parental age by birth rank was also made. The full results are not reproduced here, but the following table gives the ages of the parents of first births.

Group	Patients	Mean Age of Father	Mean Age of Mother
I	19 males ..	28.1	25.6
	14 females ..	30.4	27.6
II	30 males ..	30.1	26.6
	37 females ..	28.6	26.0
III	29 males ..	31.9	28.1
	18 females ..	31.8	26.9
Controls	28.5	25.3

This suggests an excess of elderly primiparae among the parents of female Group I children and among the parents of male Group III children.

Conclusions

An attempt has been made to provide pointers to the elucidation of the aetiology of this complex of congenital malformations. The excess of males in Groups I and III suggests that females are less susceptible to the interactions of polyfactorial genetical and environmental factors which are concerned in the pathogenesis of this sub-division. Thus, there is evidence that advanced maternal age at first birth may predispose to a Group I malformation in females and to a more severe

Group III malformation in males. In the same way other less potent factors may cause a cleft lip in males, with a lower threshold of resistance, but nothing at all in females.

The increased paternal age, in Group III especially, suggests (Penrose, 1955) that fresh paternal mutations are concerned in the pathogenesis of this condition. Such mutations might be especially important in the fathers of female patients, who are older, since it has been argued above that females may have a higher threshold of resistance to environmental and genetical factors responsible for these malformations.

There is suggestive evidence, both because of the very different sex ratio in Group II and because of the incidence of isolated cleft palate as a constituent of various complex syndromes thought to be inherited in a dominant manner, that single genes may play a large part against a background of polyfactorial genes and environmental factors in the determination of this condition. The moderately raised parental age, once again more marked for fathers than mothers, suggests that fresh mutations may play a role. Such fresh mutations both in this Group and in Group III compensate for genes lost due to early death, as in Pierre Robin's syndrome.

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