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OROFACIAL CLEFTS IN CZECHOSLOVAKIA

Incidence, Genetics and Prevention of Cleft Lip and Palate over a 19-year Period

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Abstract. The precise value of incidence was calculated based on the sample of 3660 probands with orofacial clefts born in Bohemia between 1964–1982, as all cases born in this region and time were registered. For non-syndromic cases, the incidence of cleft lip was 0.4396 per 1000 live birth, 0.7684 for cleft lip and palate and 0.6024 for isolated cleft palate. The sample of 4950 of our older probands born between 1886–1963 was added and the whole sample of 8250 individuals was evaluated with respect to sex-ratio, laterality, clinical severity, seasonal incidence and age of parents. The risk of recurrence and value of heritability were calculated as well. Based on these evaluations, a four-threshold multifactorial model for cleft lip and palate was suggested and also confirmed by our results of primary prevention of orofacial clefts using periconceptional supplementation with vitamins and folic acid.

Key words: cleft lip and palate, cleft palate, incidence, genetics, prevention.

Approximately 20 years ago, the collection of pedigrees of probands with orofacial clefts and first genetic analyses started in our genetic unit, which had been founded by one of the world's first plastic surgeons, Francis Burian. More than 10000 large pedigrees with probands suffering from congenital malformations, from which 8250 belong to orofacial clefts, made sufficient background to analyze etiology and heredity of this common malformation.

MATERIALS AND METHODS

During the past 20 years, each child born in Bohemia with cleft and its family have been examined (usually when the child is three months old) in our genetic unit in Prague. This sample, which consists of 3660 individuals, was used for estimation of incidence of cleft lip (CL), cleft lip and palate (CLP) and isolated cleft palate (CP). After addition of another sample representing 4950 of our older probands (born between 1886–1963), the sex-ratio, laterality, clinical severity, age of parents and month of birth have been evaluated from the sample of 8250 individuals with cleft. Our older probands, who were born between 1920 and 1950 (381 male and 197 female) and who had children, formed the basis for a family study. The sample also includes 87 twin pairs. The study of primary prevention of orofacial clefts by periconceptional supplementation using multivitamins and folic acid was done on the sample of 240 mothers, who previously had given birth to a child with cleft, or who themselves or their husbands had been affected with cleft.

RESULTS AND DISCUSSION

1. *Incidence*

The incidence of orofacial clefts was calculated from the sample of 3660 individuals, born with this anomaly during 1964–1982 in Bohemia. These data were collected from two sources. First, from patients coming to our unit and secondly, the data were supplemented after comparison with the governmental monitor of birth defects. In this way, practically all cases with cleft were picked up and recorded and the children were seen in our genetic unit. The total number of live births (1964–1982) in Bohemia was 1831036. When the cases with syndromes and multiple malformations were excluded, the incidence was calculated separately for each type of cleft (Table I). For non-syndromic cases, the incidence was 0.4396 (1:2275) per 1000 live birth for cleft lip, 0.7684 (1:1301) for cleft lip and palate, 1.2064 (1:828) for cleft lip with or without cleft palate and 0.6024 (1:1660) for isolated cleft palate.

The incidence of this anomaly is usually rather stable in given populations, but significant differences have been described in different races. There are many studies of incidence in Caucasians, in which the values for CL±P vary from 0.95 (22) to 1.60 (8) (4, 6, 8, 18, 19, 22, 29), as well as the values for CP vary from 1.21 (22) to 0.27 (4). These extreme values cannot be explained only by regional differences, which very probably exist. In these studies,

Table I. *The incidence of orofacial clefts in Bohemia in 1964–1982*
CL=cleft lip, CLP=cleft lip and palate, CP=isolated cleft palate

Type of cleft	No.	Total	Incidence[a] calculated from each year			Cleft : live birth
			$\bar{X}$	±	SD	
CL	805	0.4396	0.4384		0.0558	1 : 2275
CLP	1 407	0.7684	0.7640		0.0776	1 : 1301
CL+CLP	2 212	1.2081	1.2064		0.0907	1 : 828
CP	1 103	0.6024	0.5990		0.0761	1 : 1660

[a] Total number of live births in 1964–1982 in Bohemia 1 831 036.

where the highest values were found, either cases with syndromes were included, or data were collected from a small region and over a short time. An explanation for the lowest values—besides those mentioned above—may be underreporting of minor defects. Very low incidence is described in a black population (10, 15). Considering the incidence in Japanese as significantly higher in comparison with Caucasians has almost become a tradition. In contrast, the review paper by Koguchi (13) summarizing ten different Japanese studies ranging from 1953 to 1972 presented almost identical values with those obtained in the present study.

2. *Sex-ratio*

The sex-ratio values in our sample were calculated separately for the sample of total register (probands born between 1964–1982) and for the whole sample (Table II). A significantly higher proportion of males was found in CL (1.50) and CLP (2.08). The more severe forms had higher values. This corresponds with findings of other authors (13, 18). As in other studies, a prevalence of females was found in CP (0.74).

3. *Laterality of CL±P*

In the CL and CLP cases, the left side is significantly more frequently affected than the right one. The same has been found in experimental animals. It was suggested as a possible explanation that major blood vessels supplying the right side of the head of the fetus leave the aortic arch closer to the heart and more in line with blood flow, than those going to the left side (12). In our study, the left side was affected twice as often as the right (Table III) and this ratio was not influenced by clinical severity of the anomaly or by the sex of the proband.

4. *Clinical severity of CL±P*

The ratio of unilateral cases to bilateral ones is related to the severity of the affection. In our sample this ratio was 10.9 in CL and 2.5 in CLP (Table IV). By comparing sex of proband and clinical severity of his anomaly, it was confirmed that the ratio was rather stable within CL and CLP groups and was not influenced by sex of the proband. These findings are in agreement with the Hungarian study (9). Danish data (18) showed a higher proportion of unilateral cases in CL±P (4.7), which was

Table II. *Sex-ratio in orofacial clefts*
CL=cleft lip, CLP=cleft lip and palate, CL±P=cleft lip with or without cleft palate, CP=isolated cleft palate

Type of cleft	Probands					
	1964–1982			1886–1982		
	Male	Female	Sex-ratio	Male	Female	Sex-ratio
CL	497	308	1.61	1 245	831	1.50
CLP	939	468	2.01	2 197	1 034	2.08
CL±P	1 436	776	1.85	3 442	1 885	1.83
CP	467	636	0.73	1 099	1 479	0.74

Table III. *Laterality in CL±P*

CL=cleft lip, CLP=cleft lip and palate

Type of cleft	Male No.	Male %	Female No.	Female %	Sex-ratio
CL					
Sin	748	69.4	516	72.0	1.45
Dx	330	30.6	201	28.0	1.64
Total unilat.	1 078	100.0	717	100.0	1.50
Sin : dx	2.27		2.577		
CLP					
Sin	1 040	70.5	470	65.6	2.21
Dx	436	29.5	246	34.4	1.77
Total unilat.	1 476	100.0	716	100.0	2.06
Sin : dx	2.39		1.91		

plained by higher proportion of bilateral cases in CL (9.3). Data from Sweden (9) are in agreement with our data for CL (11.8), but a lower value is reported for CLP (1.7).

5. *Genealogical study*

Among the most valuable data in genetic studies are segregation ratios of non-affected and affected children and grandchildren of probands with the anomaly. In our sample, 578 probands (381 male and 197 female) had offspring. There were 855 children and 149 grandchildren altogether in this sample, of whom 41 children and 3 grandchildren were born with cleft. The probands had 1 046 siblings. The structure of this subsample is showed in Table V. The segregation ratio, which represented the risk of recurrence, has been calculated separately for subgroups divided with respect to sex of the proband and

Table IV. *Clinical severity in CL±P*

CL=cleft lip, CLP=cleft lip and palate, CL±P=cleft lip with or without cleft palate

Type of cleft	Unilat.	Bilat.	Ratio
CL			
Male	1 078	96	11.2
Female	717	68	10.5
Total	1 795	164	10.9
CLP			
Male	1 476	599	2.5
Female	716	268	2.7
Total	2 192	867	2.5
CL±P			
Male	2 554	695	3.7
Female	1 433	336	4.3
Total	3 987	1031	3.9

Table V. *Structure of the sample of probands with offspring*

Probands	Sibs	Children	Grand-children
Male (381)	537	437	64
Female (197)	509	418	85
Total (578)	1 046	855	149

severity of the affection (Table VI). A higher risk of recurrence was found when the proband was female (compared to male), as well as a higher value of risk figure, when proband had bilateral cleft (compared to unilateral cleft). Calculation of the segregation ratio according to sex of parents and children led to interesting results (Fig. 1). The highest risk was found for sons of mothers with CL±P and the lowest for daughters of fathers with CL±P. Exactly an opposite situation was found for CP. The highest value of recurrence risk was found for daughters of fathers with CP and the lowest for sons of mothers with CP.

6. *Four-threshold model of liability*

The results presented above for the sample of 5 327 probands with CL±P revealed significant differences between the four basic subgroups. These findings led us to suggest a multifactorial model of liability with four different thresholds related to sex of the proband and severity of the anomaly (25, 26). According to Carter (2)—although some contrary views have been raised by American authors, who reanalyzed classical Danish data (18)—the most economical hypothesis explaining the etiology of the majority of orofacial clefts is the multifactorial threshold model. The liability, which depends on

Table VI. *Proportion of affected and non-affected relatives of probands with respect to sex of probands and clinical severity of cleft*

Probands	Recurrence risk in % Sibs	Children	Grand-children
Male	2.75	4.47	1.12
Female	4.59	5.35	3.33
Unilat.	3.38	3.68	2.22
Bilat.	3.74	10.14	–
Total	3.44	4.80	2.01

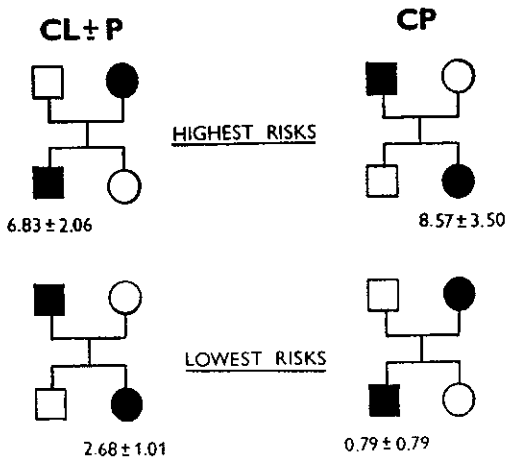

Fig. 1. Extreme values (the highest and the lowest) of recurrence risk for CL±P in pedigree with respect to sex of parents and offspring. CL±P=cleft lip with or without cleft palate, CP=isolated cleft palate.

genetic and non-genetic (exogenous) factors, is represented by a curve of normal distribution and a threshold, beyond which the individuals are affected with cleft. According to our data, 0.1208% of individuals with CL±P (Fig. 2) are above the threshold.

Different values of incidence in males (0.1531%) and females (0.0869%) subdivide the population above the threshold into two subgroups (Fig. 3). A similar situation is found, when a division is made with respect to severity of clefts (Fig. 4)—bilateral cases are more rare (0.0260%) than unilateral cases (0.0948%). Therefore, the risk of transmitting the cleft to offspring is higher than in male and in unilateral clefts (see Table VI). Combination of

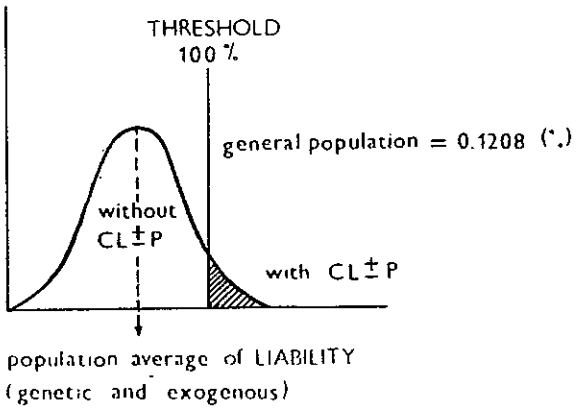

Fig. 2. Multifactorial threshold model of CL±P. CL±P=cleft lip with or without cleft palate.

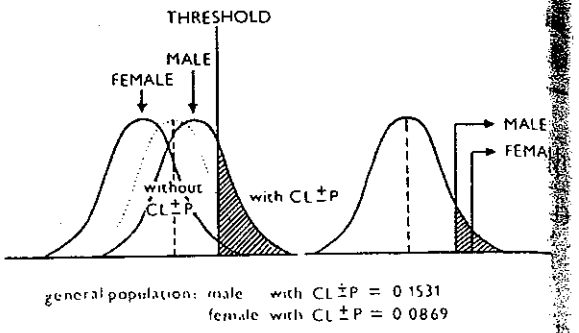

Fig. 3. Two-threshold model of liability to CL±P with respect to sex of the proband. CL±P=cleft lip with or without cleft palate.

both characteristics finally results in the four-threshold model with different thresholds for individual subgroups (Fig. 5):

1. male probands with unilateral CL±P,
2. female probands with unilateral CL±P,
3. male probands with bilateral CL±P, and
4. female probands with bilateral CL±P.

From the first to the fourth subgroup, the incidence in the general population decreases and the risk of recurrence and the value of heritability increases (Table VII). According to the definition of heritability, the proportion of exogenous etiological factors also increases with increasing heritability while the participation of exogenous etiological factors decreases. The results of our method of primary prevention of orofacial clefts (see the next paragraph) also seem to support our hypothesis of the four-threshold model of liability.

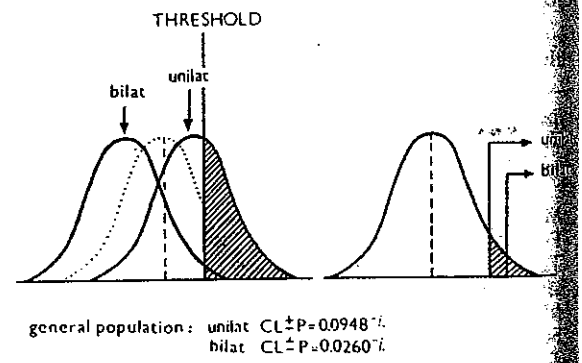

Fig. 4. Two-threshold model of liability to CL±P with respect to clinical severity of the affection. CL±P=cleft lip with or without cleft palate, unilat=unilateral CL±P, left or right, bilat±bilateral CL±P.

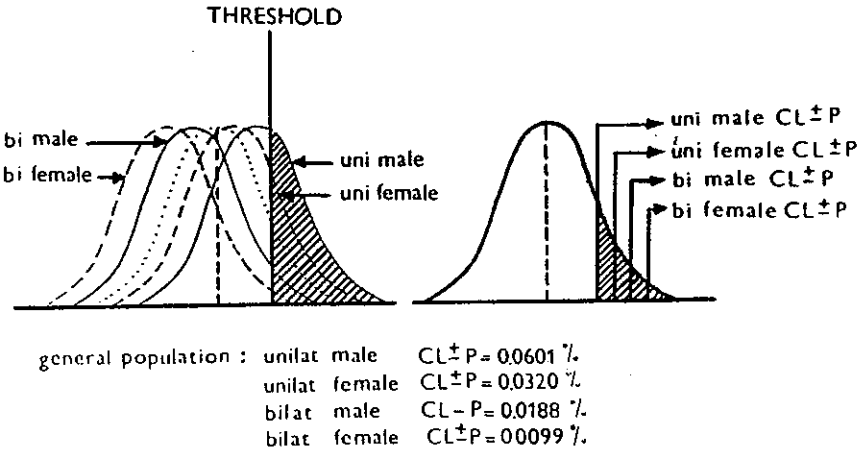

Fig. 5. Four-threshold model of liability to CL±P with respect to sex of the proband and clinical severity of the affection. CL±P=cleft lip with or without cleft palate; uni, unilat= unilateral CL±P, left or right; bi, bilat=bilateral CL±P.

7. *Primary and secondary prevention*

The role of environmental factors including diet and possibilities of prenatal diagnosis in relation to prevention of craniofacial malformations were discussed by Poswillo (21) and more recently for craniofacial malformations by Johnston (11).

Although the ultrasound technique enables us to recognize individual structures in the craniofacial region of the fetus in utero, and this method is still developing rapidly, at present the only method of prenatal diagnosis, by which the orofacial clefts can be safely diagnosed, is the visualization fetoscopy. In agreement with the rules for indicating visualization fetoscopy (27), the cases in which the recurrence risk was above 10% (e.g. high risk families with cleft as well as the autosomal dominant and autosomal recessive syndromes), were recommended for secondary prevention utilizing fetoscopy. 52 cases were recommended for visualization fetoscopy from our unit, of which 22 cases were from highrisk families, cases of Treacher-Collins syndrome, Majewski syndrome, lobster-claw syndrome, Van der Woude syndrome and others.

An association between nutritional deficiency in pregnant animals and birth defects in their offspring was first reported by Warkany & Nelson (28). Since that time, several tests of dietary prevention of birth defects in man were carried out. Vitamins and folic acid were used in prevention of orofacial clefts by Peer et al. (20), Douglas (5), Conway (3), Briggs (1), Gabka (7) and von Kreybig & Stoeckenius (14), and recently also in neural tube defects by Laurence et al. (16, 17) and Smithells et al. (23).

Our method is based on the hypothesis that environmental triggers, which probably play a very important role in the etiology of clefts, may be suppressed or inhibited. We used periconceptional supplementation with vitamins and folic acid. Our

Table VII. *Main characteristics of four individual subgroups of orofacial clefts*

	Subgroups			
	Unilateral		Bilateral	
Character	Male	Female	Male	Female
Incidence in general population (in %)	0.0601	0.0320	0.0188	0.0099
Risk of recurrence in 1st degree relatives	2.85	4.32	6.57	8.89
Heritability	0.6385	0.7682	0.8779	0.8779

Table VIII. *Prevention of CL±P using periconceptional vitamin and folic acid supplementation*

	Prevention			Control			Results		
		With clefts			With clefts		No. of expected cases	No. of observed cases	Difference
Proband	Total	No.	%	Total	No.	%			
Unilateral									
Male	82	0	–	973	28	2.88±0.54	2.36	–	-2.36^{+}
Female	58	1	1.72±1.72	59	27	4.55±0.88	2.64	1	-1.64^{++}
Bilateral									
Male	30	1	3.33±3.33	218	14	6.42±1.72	1.93	1	-0.93^{+++}
Female	14	1	7.14±3.33	117	8	6.48±2.42	0.96	1	+0.04
Total	184	3	1.63±0.94	1 901	77	4.05±0.46	7.45	3	-4.45^{++++}
Cleft in pedigree	56	1	not evaluated statistically						

Fisher's exact one-tailed test: $^{+}$ p=0.1006, $^{++}$ p=0.2897, $^{+++}$ p=0.4361, $^{++++}$ p=0.0659. χ^2: $^{+}$ 2.424 p=0.05975, $^{++}$ 0.92 p=0.1678, $^{+++}$ 0.443 p=0.2529, $^{++++}$ 2.663 p=0.0514.

present data evaluating 240 pregnancies, in which primary prevention was used, confirmed the positive results published previously (24). In agreement with the four-threshold model, the best results were obtained in the most frequent subgroup, where the proportion of exogenous factors is the highest, i.e. in subgroups of male probands with unilateral clefts (Table VIII). Still more data are necessary to confirm our hypothesis. However, if we consider the results of our method, results of prevention of neural tube defects, experimental and human data in orofacial clefts, it seems to be one of the promising ways of to decreasing the frequency of clefts in families at risk.

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