Cleft Uvula: Prevalence and Genetics

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The *prevalence* of cleft *uvula* (CU) was determined among 70,359 school children 6–18 years of age; 90 children having the condition were chosen as probands for a *family study*. Prevalence of CU was 0.44 per cent with no sex differences. The Non-Ashkenazi group had a higher prevalence than the other population groups. The prevalence of CU in parents and siblings was 7.7 per cent and 7.5 per cent respectively. The findings from the family study support the hypothesis of a *polygenic* mode of *inheritance* for CU. The prevalence of *cleft palate* and agenesis of upper *lateral incisors* in the families studied did not differ from that expected in the general population.

Introduction

The prevalence of cleft uvula (CU) has been found to vary among different population groups (Cervenka and Shapiro, 1970; Richardson, 1970; Schauman, Peagler, and Gorlin, 1970; Jarvis and Gorlin, 1972). It has also been suggested that this condition is a minor manifestation of cleft palate (Cervenka and Shapiro, 1970) and that the varying prevalence might be correlated to the prevalence of cleft palate in different populations (Cervenka and Shapiro, 1970; Richardson, 1970).

Meskin, Gorlin, and Isaacson (1965) concluded that CU is transmitted as an autosomal dominant trait with limited penetrance. Cervenka and Shapiro (1970) suggested that their findings are consistant with polygenic inheritance. Another study (Shapiro et al., 1971) has supported the contention that CU is a microform of facial clefts and that the findings are most consistent with a quasicontinuous polygenic basis for these conditions.

The different population groups among Jews in Israel allow for the examination of the hypothesis that the prevalence of CU varies among different ethnic groups. Another purpose of this study was to investigate the mode of inheritance of the condition.

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Methods

The determination of the prevalence of CU formed a part of an epidemiologic and genetic study of various oral abnormalities among Jews in Israel (Chosack, Zadik, and Eidelman, 1974). In this investigation, 70,359 children, six to 18 years old were examined. These were all the children attending schools and receiving dental care from the Tel-Aviv and Jerusalem municipalities. The dentists were trained and any disagreements in diagnostic criteria clarified by means of lectures, a printed manual, and group examinations of samples of the children. This standardization was repeated three times before the examinations took place and twice during the examination period.

The criteria for diagnosing CU was a distinct bifurcation of at least one fourth of the total length, evident during visual examination. This corresponds with types C and D of the classification used by Meskin, Gorlin, and Isaacson (1964). It was decided to use these criteria when it was found that it was difficult to reproduce diagnoses among examiners when type B of Meskin, Gorlin, and Isaacson (1964) was also included. An extremely good agreement was found among the examiners when these criteria were used. However, no statistical assessments of inter-examiner agreement were carried out. The age and sex of the children, country of birth of the father, and the condition diagnosed, were recorded.

In the analysis the children were divided

into three groups, determined by the country of birth of the father: Israeli children whose fathers were born in Israel; Ashkenazi children whose fathers were born in countries where the majority of the Jewish population trace their origins to Central and Eastern Europe; and Non-Ashkenazi children whose fathers were born in North Africa, Asia, Yugoslavia, Bulgaria, Greece, Turkey and Albania.

The major reason for the choice of the father's origin was that the information on the 70,000 children examined was obtained from school records which follow the method used by the Central Bureau of Statistics in Israel whereby the families' origins are determined by those of the fathers. Ninety per cent of grooms from Non-Ashkenazi origin and 82 per cent of grooms from Ashkenazi origin are married to brides of the same origin as the grooms. Most of the fathers born in Israel would, by ancestry, fall into the Ashkenazi or Non-Ashkenazi groups. Intermarriage among Israeli-born males from Ashkenazi and Non-Ashkenazi ancestry differs from that of the rest of the population. Twenty-six per cent of Israel-born grooms who had Non-Ashkenazi ancestry married brides of Ashkenazi origin; 16 per cent of Israel-born grooms with Ashkenazi ancestry married Non-Ashkenazi brides (Statistical Abstracts of Israel, 1966). It must be realized that the groups classified as Israeli, Ashkenazi, and Non-Ashkenazi contain within themselves a large number of smaller sub-groups. Only in the Non-Ashkenazi can these sub-groups be clearly identified. Intermarriage within the Israeli and Ashkenazi groups has clouded the borders between their different sub-groups.

Of those children having CU, probands were selected for the family study. This investigation reporting on cleft uvula was only part of a larger survey on various developmental anomalies, and sampling was necessary in order to keep to the time and funds available. The investigators, in consultation with a statistician, decided that about 100 families would provide the information required. After examining the first 10,000 children, a forecast of the total expected prevalence was made, and a random number selection from the affected was arranged. When more than one sibling of the family was affected and detected independently, only the first detected sibling was eligible as a proband for the family study. After some elimination from the 100 families chosen because of refusal by family members, doubtful paternity, or adoptions, families from 90 probands of the total 309 children affected by CU formed the population of the family study.

The first degree relatives, that is parents and siblings, were examined in their homes by the same dentists who participated in the prevalence study. The presence of clefts of lip or palate or agenesis of upper lateral incisors were recorded. Two groups of siblings were analyzed further: group A, being those siblings from families in which neither parent had the condition and group B being those siblings in whose families at least one of the parents had the condition. Family members not available for the examination were not included in the family analysis.

The test for comparison of two observed frequencies with the normal approximation (Brownlee, 1960) was used for the statistical analysis of the data at the 95 per cent level of significance. When comparing group A and group B siblings, the test was done with correction of continuity.

Results

Prevalence in the total population was 0.44 per cent (Table 1). No differences were found between the sexes. The Non-Ashkenazi group had a significantly higher prevalence than the Israeli and Ashkenazi groups. The Non-Ashkenazi males had a significantly higher prevalence than males of the other two groups, but there were no significant differences among females. The prevalence was higher in the 12 and above age group. However, the 10-to-11-year age group had a lower prevalence than the eight-to-9-year-olds. The findings in the Non-Ashkenazi subgroups are presented in Table 2. The prevalence among the subgroups ranged from 0.22 per cent to 0.95 per cent in males, and from 0.13 per cent to 0.86 per cent in females. Subgroup D (Iran, Afghanistan, India, Pakistan) had the highest prevalence in both sexes. The descending order of prevalence among the subgroups was not the same among the sexes. In males, subgroup D was followed by subgroups H, B, and E, whereas, in females, subgroup D was followed by subgroups A, B, and C in order of prevalence.

TABLE 1. Prevalence of cleft uvula by age, sex and country of birth of father.

age		Israel		Ashkenazi		Non-Ashkenazi		total	
		male	female	male	female	male	female	male	female
7 and below	Sample	2,306	2,255	2,407	2,343	3,278	3,354	7,991	7,952
	Number	3	5	3	7	13	6	19	18
	%	0.13	0.22	0.13	0.30	0.40	0.18	0.24	0.23
8–9	Sample	2,351	2,127	2,778	2,565	3,392	3,100	8,521	7,792
	Number	12	6	7	3	18	24	37	33
	%	0.51	0.28	0.25	0.12	0.53	0.77	0.43	0.42
10–11	Sample	1,908	1,835	3,284	3,109	3,374	3,209	8,566	8,153
	Number	6	4	6	6	20	6	32	16
	%	0.31	0.22	0.18	0.19	0.59	0.19	0.37	0.20
12 and above	Sample	2,049	2,166	4,147	4,437	4,175	4,410	10,371	11,013
	Number	11	12	30	32	37	32	78	76
	%	0.54	0.55	0.72	0.72	0.89	0.73	0.75	0.69
Total	Sample	8,614	8,383	12,616	12,454	14,219	14,073	35,449	34,910
	Number	32	27	46	48	88	68	166	143
	%	0.38	0.32	0.37	0.39	0.62	0.48	0.47	0.41
Grand Total	Sample	16,997		25,070		28,292		70,359	
	Number	59		94		156		309	
	%	0.25		0.37		0.55		0.44	

TABLE 2. Prevalence of cleft uvula by sex and country of birth of father in the non-Ashkenazi subgroups

country of birth of father	male			female		
	sample size	children affected	%	sample size	children affected	%
(A) Syria, Lebanon, Jordan	1,051	5	0.48	1,006	7	0.70
(B) Iraq	3,621	25	0.69	3,534	19	0.54
(C) Saudi Arabia, Yemen, Aden	1,377	3	0.22	1,380	7	0.51
(D) Iran, Afghanistan, India, Pakistan	2,007	19	0.95	1,977	17	0.86
(E) Morocco	2,767	16	0.58	2,670	8	0.30
(F) Algeria, Tunisia, Libya	810	3	0.37	794	1	0.13
(G) Egypt, Sudan	802	3	0.37	796	4	0.50
(H) Turkey, Yugoslavia, Bulgaria, Greece, Albania	1,784	14	0.79	1,916	5	0.26
Total	14,219	88	0.62	14,073	68	0.48

TABLE 3: Prevalence of cleft uvula in family members of probands

	no. examined	affected	
		number	%
Parents	169	13	7.7
Fathers	81	8	9.9
Mothers	88	5	5.7
Siblings	200	15	7.5
Brothers	102	7	6.9
Sisters	98	8	8.2
Siblings group A (both parents unaffected)	155	11	7.1
Siblings group B (at least one parent affected)	24	3	12.5

The prevalence of CU in parents and siblings of probands (Table 3) was 7.7 per cent and 7.5 per cent respectively, significantly higher than that found in the general population (0.44%). Prevalence in group B siblings (12.5%) was higher than that in group A siblings (7.1%), but the difference was not statistically significant. Of the 169 parents and 200 siblings examined, one sister was found to have cleft palate; two fathers (2.5%), two mothers (2.3%), and two brothers (2.0%) had missing upper lateral incisors. Of all first degree relatives examined, 1.6% had missing upper lateral incisors.

Discussion

Prevalence. The prevalence of CU in the total population (0.44%) lies between the prevalence of 0.27% found in the corresponding types C and D of Meskin, Gorlin, and Isaacson (1964) and of 0.58% found in Czechoslovakia (Tolarova, Havlova, and Ruzickova, 1967). The prevalence reported for American Indians (2.8%) was much higher (Cervenka and Shapiro, 1970). When a separate analysis was carried out for the three major groups making up this population, significant differences were found. Similarly, when the Non-Ashkenazi group was analyzed in the different subgroups, variations in the prevalence of CU were found.

If it is accepted that CU is a genetic condition, then the various populations would have different gene frequencies.

The Israeli group is actually composed of people of Ashkenazi and Non-Ashkenazi origin. The prevalence of CU in the Israeli group was lower than would be expected. The effect of environmental factors and intermarriage among different populations on the frequency of CU deserves further investigation.

The results presented in Table 1 seem to suggest an increase in prevalence with age. However, this increased prevalence could most probably be attributed to the more apparent bifurcation in a larger uvula. An additional factor could be the more difficult task of exposing the uvula without contraction of its muscles in younger patients. It is possible that, unless specifically looked for in infants by the examining physicians, a bifid uvula may pass undetected.

Genetics. The prevalence of CU in the parents and siblings was significantly higher than that found in the general population indicating that this condition is familial. The findings in first degree relatives are not compatible with autosomal recessive traits and would necessitate postulating an improbably low penetrance (15%) to be compatible with an autosomal dominant mode of transmission.

Edwards (1960) stated that the frequency among first-degree relatives in polygenic traits should approach the square root of the population frequency. The 7.6 per cent prevalence found in parents and siblings is close to the theoretical 6.6 per cent which is the square root of 0.44 per cent, the prevalence in the population. Although not statistically significant, there was a tendency for a higher prevalence in group B siblings, a finding that is a characteristic of polygenic conditions (Carter, 1965). The findings in this investigation support the hypothesis (Cervenka and Shapiro, 1970; Shapiro et al., 1971) that CU is a polygenic trait and not a simple Mendelian condition.

Cleft Palate. It has been suggested that CU is a microform of cleft palate (Meskin et al., 1964; Tolarova et al., 1967; Shapiro et al., 1971). Gorlin and Pindborg (1964) stated that, if the parents of a child affected with cleft palate are normal, the risk to siblings is about 2 per cent, and if both a parent and a child are affected, the risk is 15 per cent. Among the 24 siblings in group B and the other 176 siblings (155 group A siblings and 21 unclassified), at least seven cases (15% of group B + 2% of group A) of isolated cleft palate should be expected if CU is a mild expression of cleft palate. Only one sibling was found to have cleft palate, this being the only case among the 459 persons in the families in which there was proven CU. This is not significantly different from the expected prevalence in the general population. These findings suggest that either CU is a separate entity or that, if it is part of a polygenic continuous trait with cleft palate, the difference between the threshold values for both conditions is of such dimensions that the risk of cleft palate in family members of probands with CU is not different from that of the general population.

Upper lateral incisors. A higher frequency of agenesis of upper lateral incisors has been reported in parents and siblings of children with CU (Meskin et al., 1965). This was not confirmed by the findings in this study in which the prevalence of missing upper laterals in first degree relatives was 1.6 per cent as compared to 2.1 per cent found in the general population (Eidelman, Chosack, and Rosenzweig, 1973).

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