Journal of IMAB - Annual Proceeding (Scientific Papers) 2008, book 2

CLINICAL AND GENETIC PECULIARITIES OF ISOLATED CLEFT PALATES

Vera Krumova
Department of Orthodontics, Faculty of dental Medicine,
Medical University – Sofia, Bulgaria

SUMMARY

The systematic investigations on genealogical data of children with clefts have revealed that there is clinical-genetic heterogeneity between cleft lips and/or palates (CL/P) and isolated cleft palates (CP). Isolated cleft palates are often a constituent part of syndromes. These clefts are most frequently found in Pierre Robin syndrome, as this syndrome is more typical for the girls than the boys. The following micro-symptoms were observed among the relatives of children with CP: bifid uvula (BU), palatal defect, submucous cleft, intrauterine healed harelip and cleft nose. The results have shown that 43.4% of the children of our sample manifested accompanying malformations and syndromes, which means that almost every second child with CP has additional congenital diseases. Among the examined relatives, 18.81% demonstrated various types of micro-symptoms. The genetic-mathematical data processing has revealed that only isolated CP demonstrated polygenic type of inheritance, while CP with accompanying malformations approached mostly the autosomal-dominant type of inheritance.

Key words: cleft palate, micro-symptoms, heredity, syndromes.

The systematic investigations on genealogical data of children with clefts have revealed that there is clinical-genetic heterogeneity between cleft lips and/or palates (CL/P) and isolated cleft palates (CP). It is determined by the significant difference between the incidences of the two types of clefts and their distribution by gender showing prevalence of CL/P in boys and CP in girls. Fogh-Andersen [10] has anamnesticaly proven cleft clinical-genetic heterogeneity in 703 families, whose children with clefts underwent surgical interventions in a Copenhagen clinic. This heterogeneity has been expressed by the different percentage of aggravated familial history – 36.7% cleft inheritance in CL/P families and 19.0% in CP families. The different percentage of aggravated heredity has been also confirmed by the studies of other authors [13]. Wolf et al. [15] supporting the thesis of gender-modified polygenic heredity of clefts, have concluded that the risk of cleft occurrence is two-fold higher for the children of women with CL/P. According to them, more than 10% of the sons of these women would possibly manifest clefts. They have stated that no daughter with a cleft was born by any of these patients. Regarding the various genetic dependence of clefts, the authors have suggested that studies on women with clefts would be of particular interest.

Cleft palates (CP) are often a constituent part of syndromes. A higher incidence of accompanying malformations in CP children has been also reported by other authors [2, 8]. Cleft palates are most frequently found in Pierre Robin syndrome, as this syndrome is more typical for the girls than the boys [4]. The type of inheritance and cleft genetic heterogeneity could be clarified through systematic investigations on genealogies of CP children, where the various degrees of minimal manifestations/micro-symptoms are assessed.

Tolarova [5, 6, 7] has examined the bifid uvula (BU) as the only micro-symptom in relatives of CP individuals. According to her, the other micro-manifestations of cleft palates, such as gothic palate, asymmetric shape of the upper lateral incisives and asymmetry of nose could be, from genetic point of view, associated signs but not genuine micro-manifestations of these clefts. Meskin, Corlin and Isaakson [13] have also observed the bifid uvula as a micro-symptom of the cleft palate (CP).

Fukihara and Saito [11] have suggested that examination of micro-symptoms could increase up to 50% the incidence of aggravated familial history cases in all types of clefts.

The pathomorphologic changes of palate have been also reported as micro-symptoms of CP. The observed changes in hard palatal development are described as "submucous clefts". The clinical examinations of submucous clefts and their consideration as a micro-symptom of CP have been reported by many authors [6, 12]. Calnan [9] has described the submucous cleft as a triad of symptoms including bifid uvula, shortened soft palate with muscular diastasis along the median line (i.e. thin median suture) and a groove in the posterior palatal portion. The combination of these symptoms is not obligatory for the individual case.

Demikova et al. [3] have related cleft ethiopathogenesis with the basic concept of micro-

symptoms, on one hand, as manifestations of a mutant gene or gene's altered expression and on the other – as caused by the sub-threshold accumulation of genes as factors in the multifactor etiology of clefts. According to these authors, the expressed nasality could be a clinical manifestation of the cleft palate since soft palate malfunction could be explained with the presence of a cleft palate or a submucous cleft.

It could be suggested that the variability of gene activity causes the various clinical manifestations of clefts. Micro-symptoms could be considered in relation to medical-genetic consultation improvement and risk factor evaluation in families of CP children.

The aim of this study was to examine the peculiarities of cleft palate manifestations and genetic determination.

MATERIAL AND METHODS

The study material involved 17 CP children with no accompanying malformations or syndromes and 13 CP children with accompanying malformations or a diagnosed syndrome observed during the performed population study on cleft incidence in Central West Bulgaria [4]. In 10 of the CP children, a genealogic study involving 101 relatives was carried out as maxillary casts for anthropological examinations were taken. Extra-oral micro-symptoms, such as intrauterine healed harelip and cleft nose (after Tolarova's method), and intra-oral micro-symptoms, such as bifid uvula (after Meskin's method) and palpatory diagnosed mucosal depression along the palatal suture (submucous cleft, SMC) (after Ritter and Calnan's method) were examined [9, 14].

Genetic-mathematical methods were applied for determination of the type of inheritance in the genealogies of children with CP [1].

RESULTS AND DISCUSSION

The distribution by gender was 13 boys: 17 girls in the examined 30 children with CP, the isolated CP being more frequent among the female children. **Table 1** represents the distribution of accompanying malformations and syndromes among CP children.

30.0% of the children with isolated CP suffered from Pierre Robin syndrome and 13.3% manifested other accompanying malformations and congenital diseases. These data correspond to the publications of Meskin et al., Genchik et al., Fara et al. [13, 2, 8].

The inclusion of the cleft palates (CP) with accompanying malformations and diagnosed syndromes in a separate group was imposed by the possibility for their different type of inheritance [2], as well as by the increasing number of reports describing new combinations between these clefts and various accompanying malformations.

In our study sample, 43.3% of the children suffered from accompanying malformations and syndromes, which means that almost every second child with CP has additional congenital diseases. This method of differentiation is of great significance for the medical-genetic consultations [7].

The investigations on the genealogies of 10 CP children revealed the following extra- and intra-oral micro-symptoms (**Table 2**).

The results showed that in 18.81% of the relatives, various micro-symptoms, mostly bifid uvula and submucous cleft (13.85%) were observed. The clinical manifestations of the most common micro-symptoms are represented on **fig. 1 and 2**.

On the basis of performed clinical and anthropological examinations, the genetic-mathematical processing of data revealed that in isolated cleft palates, hereditary multiple genes determined predisposition existed, which suggests the polygenic type of heredity of these clefts. In the group of children with CP and accompanying malformations, the genetic-mathematical processing of data showed that the type of disease transmission approached mostly the autosomal-dominant type of heredity.

These results for the type of heredity of the different cleft palates suggest that during medical-genetic consultations, a thorough analysis of cases and reconstruction of family trees are necessary in order not to omit the micro-symptoms or accompanying malformations, which could be crucial for the risk factor determination in individual cases.

Table 1. Distribution of accompanying malformations and syndromes among children with cleft palates (CP)

Type of cleft	No accompanying malformations	Pierre Robin syndrome	Other syndromes	Accompanying malformations and congenital diseases	Total
Number	17	9	1	3	30
%	56,7	30,0	3,3	10,0	100,0

Table 2. Distribution of micro-symptoms among the examined relatives of children with cleft palates (CP)

Relatives (total number 101)	BU	Palatal defect	IUH harelip	Cleft nose	Total
Number	8	7	2	2	19
%	7.92	6.93	1.98	1.98	18.81

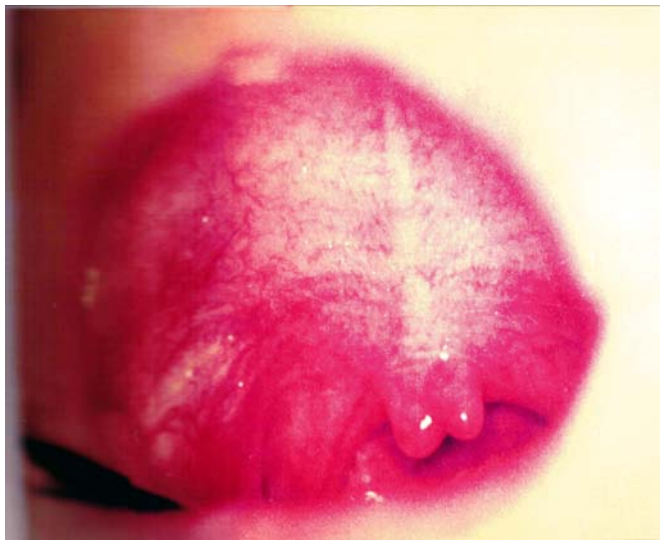

Fig. 1. Bifid uvula

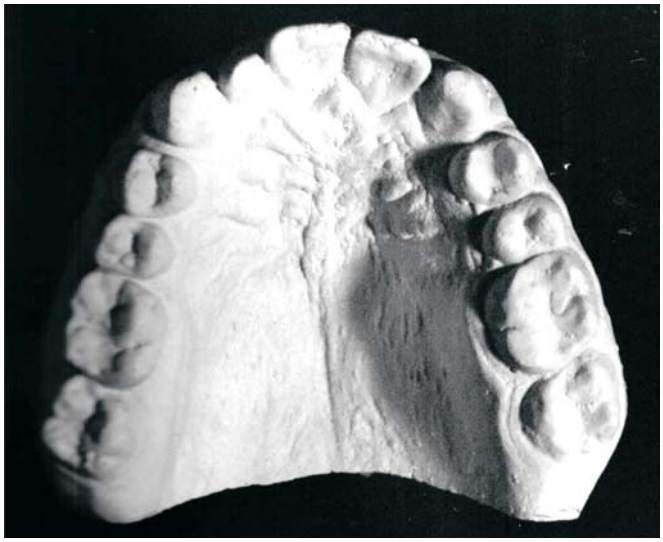

Fig. 2. Submucous cleft palate

REFERENCES

1. Абаджиев, М. Клинико-генетични методи в лекарската практика. Научен обзор. С., 1973, с. 132.
2. Генчик, А. и Л. Кадаши. Расщелины губы и неба как составная часть симптоматологии различных синдромов. Acta Chir. Plast., 22, 1980, 4, 169—173.
3. Демикова, Н. С. и Л. В. Макаренкова. Популационные и семейные частоты оро-фациальных аномалий, рассматриваемых как микропризнаки расщелин. — Генетика, М., 1983, 4, 679-684.
4. Крумова, В. Клинико-генетични проучвания при деца с цепки в челюстно-лицевата област. Дисерт., С., МУ, 1987, 237 с.
5. Толарова, М. Генеалогический анализ изолированной расщелины неба. Acta Chir. Plast., 11, 1969, 2, 93-96.
6. Толарова, М. Микроформы расщелин губы и неба. Acta Chir. Plast., 11, 1969, 2, 82-92.
7. Толарова, М. Эмпирические оценки риска для медико-генетической консультации расщелин. Acta Chir. Plast., 14, 1972, 4, 216-218.
8. Фара, М. и И. Гривникова. Присуствие расщелины неба (губы и неба) пхри синдромах и атипических расщеплениях лица. Acta Chir. Plast., 14, 1972, 1, 13-21.
9. Calnan, J. et al. Submucous cleft palate. Brit. J. Plast. Surg., 9, 1954, 6:264-282.
10. Fogh-Andersen, P. Genetic and non-genetic factors in the etiology of facial clefts. Scand. J. Plast. Reconstr. Surg., 22, 1967, 1:25-35.
11. Fukuhara, T. and Sh. Saito. Possible carrier status of hereditary cleft palate with cleft lip: report. Bull. Tokyo Med. Dent. Univ., 10, 1963, 1:333-341.
12. McWilliams, B. J. Submucous clefts of the Palate: How likely are they to be symptomatic? Cleft Palate-Craniofacial Journal, 28, 1991, 3:247-251.
13. Meskin, L. H. et al. Epidemiologic relationship of age of parents to type and extent of facial clefts. Acta Chir. Plast., 10, 1968, 4:229-239.
14. Ritter, R. Zur Theorie der unttauterin “verheilten” Lippen-Kiefer-Gaumen-Spalten. Fortschritte der Kieferorthopadie, 25, 1964, 396-403.
15. Woolf, C. MC et al. Cleft lip and palate in parent and child. Plast. Reconstr. Surg., 44, 1969, 5:436-440.

Address for correspondence:
Dr Vera Krumova, PhD
Department of Orthodontics, Faculty of Dental Medicine
1, St. G. Sofiyski Blvd., 14 31 Sofia
Phone: +359/888 215 791;
E-mail: krumovav@abv.bg