# ESTIMATION OF RECURRENCE RISK AND GENETIC COUNSELLING OF FAMILIES WITH EVIDENCE OF ISOLATED (UNSYNDROMIC) CLEFT LIP AND PALATE IN SUCEAVA COUNTY, ROMANIA

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**Abstract**: Cleft lip and/or palate are the most frequent facial congenital malformations and represent a dramatic situation at birth, which involves important functional, aesthetic, psychological and social impairment that motivates the necessity of a thorough genetic study in the view of genetic counselling. We have studied the families of 100 children with clefts born during the years 1985-1996 in Suceava county and selected from the evidences of the Children Hospital Suceava. The recurrence risk was determined in accordance with the rules of calculation for multifactorial inheritance; it varied between 2 – 5% for the majority of cases (77%) which corresponds to a small risk degree; only in 23% of cases the risk varied between 6 – 15% which corresponds to a medium risk degree.

## INTRODUCTION

Cleft lip and/or palate are congenital malformations determined by genetic and ecological factors which trigger defects of confluence between the facial buds during the 5th and the 8th week of intrauterine life.

The necessity of the genetic study of clefts is motivated, partly, by the fact that they are the most frequent congenital malformations of the face and, partly, by the fact that clefts are a dramatic situations at birth, with important functional, aesthetic, psychological and social consequences. Being a real problem of public health, the genetic counselling is essential to improve population's health through the reduction of abnormal genes frequencies.

These reasons determined us to initiate a large genetic study of the families living in Suceava county which had a new-born with isolated (unsyndromic) cleft lip and/or palate during the interval 1985-1996.

## MATERIALS AND METHODS

We have studied the families of 100 new-borns with isolated cleft lip and/or palate (from which eight were still-born) registered between 1985 and 1996 in Suceava county. The cases were selected from the evidences of the Children Hospital Suceava.

The methods of study consisted of:

- The genetic consult, including the family inquiry, the clinical and paraclinical examination.
- The positive diagnose based on symptom- syndrome diagnose keys, also helped by expert computer-based search systems (POSSUM, LDDB).
- The drawing of genealogical tree (pedigree)
- The estimation of the genetic risk of recurrence
- The proper genetic counselling.

## RESULTS AND DISSCUSIONS

Isolated cleft lip and/or palate have a multifactorial aetiology, with an important genetic component (more than 50% in the majority of cases), and, in consequence, they are not following the rules of monogenic inheritance, demonstrating nonmendelian transmission patterns.

The estimation of recurrence risk for clefts is a compulsory stage in the view of a correct genetic counselling; this is done, according to most authors (Fraser, 1970; Melnick şi Bixler, 1980; Covic, 1982; Kelly, 1980; Harper, 1984), in accordance with some empirical risks tables (table 1 and 2).

Table 1: The risk of recurrence for isolated cleft lip and/or palate (Tolarova, 1972)

| Affected persons in family | | The risk of recurrence for cleft lip with or without cleft palate (%) | The risk of recurrence for isolated cleft palate (%) |
|---|---|---|---|
| **NORMAL PARENTS** | | | |
| **Affected children** | **Normal children** | | |
| **1** | **0** | **4** | **3,5** |
| **1** | **1** | **4** | **3** |
| **2** | **0** | **14** | **3** |
| **ONE AFFECTED PARENT** | | | |
| **Affected children** | **Normal children** | | |
| **0** | **0** | **4** | **3,5** |
| **1** | **0** | **12** | **10** |
| **1** | **1** | **10** | **9** |
| **2** | **0** | **25** | **24** |
| **BOTH PARENTS AFFECTED** | | | |
| **Affected children** | **Normal children** | | |
| **0** | **0** | **35** | **25** |
| **1** | **0** | **45** | **40** |
| **1** | **1** | **40** | **35** |
| **2** | **0** | **50** | **40** |

Many studies (Fraser, 1970; Hanson and Murray, 1990; Christensen and Mitchell, 1996) proved that the isolated cleft palate is transmitted according different patterns, so on the genetic risks must be also differentiated.

The differences between the recurrence risks in males and in females are minimal, but like in all cases of polygenic determinism the presence of other affected relatives will significantly increase the risks (table 2)

Table 2: The risk of recurrence for isolated cleft lip and/or palate (Harper, 1986)

| **RELATION WITH THE PROBAND** | **Recurrence risk (%)** | |
|---|---|---|
| | **cleft lip with or without cleft palate** | **isolated cleft palate** |
| **Brothers (general risk)** | 4 | 1,8 |
| **One brother** | 2,2 | - |
| **Two brothers** | 10 | 8 |
| **Brother and parent** | 10 | - |
| **A child** | 4,3 | 3 |
| **Relative (second degree)** | 0,6 | - |

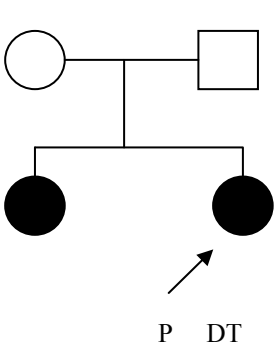
| RELATION WITH THE PROBAND | Recurrence risk (%) | |
|---|---|---|
| | cleft lip with or without cleft palate | isolated cleft palate |
| Relative (third degree) | 0,3 | - |
| Riscul în populaţia generală | 0,1 | 0,04 |

From the tabels 1 and 2, as well as from other data from literature, we have extracted the following statements:

- ✓ Two healthy parents with an affected child have a general risk of 3,3% for another affected offspring;
- ✓ The risk seems to be influenced by the sex of the affected child (Melnick et al, 1980) being slightly increased for female affected offspring;
- ✓ The recurrence risk triples (12 –14%) after the birth of two affected children;
- ✓ An affected parent has a risk of 4% to have an affected offspring; if a child with cleft lip and /or palate is borne, the risk for a new pregnancy will be 3-4 times bigger; after two affected offspring the risk becomes 25%;
- ✓ A healthy person with an affected brother/sister as a risk of 3-7% for affected offspring;
- ✓ The recurrence risks for isolated palate clefts are slightly smaller than those for labio-palatine clefts: between 1/50 (2%) (Bixler, 1981) and 3-3,5% according to Tolarova or Harper;
- ✓ The risk is also influenced by the gravity of the clefts: the risk doubles for bilateral labio-palatine clefts.

In accordance with Bixler (1981) we can strongly affirm that, because of the aetiological heterogeneity, it is difficult to give a precise genetic counsel.

In our study, as an argument for the genetic multifactorial inheritance, the familial distribution was certified in 9 cases (9%); we appreciated that this result is an undervaluation of the real data (some microforms could be lost) because the family inquiry wasn’t realised directly by discussion with all relatives, but only with one parent.



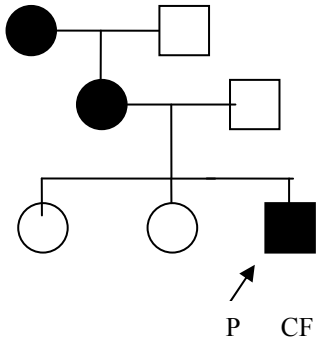




Figure 1: Two of the 12 familial cases of cleft lip and palate: DT – born in 1988, with isolated cleft palate and CF - born in 1991, with unilateral (left) cleft lip and palate.

A major objective of our study was to estimate a correct recurrence risk to perform an accurate genetic counsel (table 3); for the majority of the studied cases (close to 77%) the recurrence risk was considered small (2- 5%); only in 23% of cases the risk was considered medium (6-15%).

Table 3: The genetic recurrence risk in the families of the 100 studied cases.

| Cleft type | Parents | Proband sex | Localisation | Cleft type | Nr. of Cases | Risk of recurrence |
|---|---|---|---|---|---|---|
| Cleft lip +/- cleft palate | Healthy + 1 affected offspring | M | Unilat | DL<br>DLP | 18<br>10 | 2,2-4,7 |
| | | M | Bilat | DL<br>DLP | 4<br>9 | 6-7 |
| | | F | Unilat | DL<br>DLP | 8<br>9 | 4-5,6 |
| | | F | Bilat | DL<br>DLP | 3<br>6 | 6-8,4 |
| | Healthy + 1 affected offspring + 1-2 affected relatives (II-III degree) | M | Unilat | DLP | 3 | 2,9 – 5,3 |
| | Healthy + 2 affected offspring | M | Unilat<br>Bilat | DL<br>DLP | 2<br>3 | 10-14 |
| | 1 affected parent + 1 affected offspring | F | Bilat | DLP | 2 | 10-12 |
| Isolated cleft palate | Healthy + 1 affected offspring | M | | | 7 | 1,7-3,8 |
| | | F | | | 15 | 1,8-3,7 |
| | Healthy + 2 affected offspring | F | | | 1 | 8 |

If the recurrence risk could be calculated “at cold”, the proper genetic counselling was modulated and personalised in accordance with the degree of the handicap, with the therapeutical possibilities, with the age and intellectual level of the parents, with the presence of pregnancy and its stage, with the psychological balance and the moral and religious concepts of the couple.

The counsel was non directive, explicit, objective and convincing; it tried to eliminate the possible sentiments of culpability of the parents. Those who decided the future of the pregnancy with risk were only the parents; we tried to be an impartial informer.

The most frequent asked question was “which is the acceptable risk?”; we have tried to explain clearly the degrees of risk, and we always remembered that every healthy couple has a risk of 1.3% of having an offspring affected by a congenital malformation.

We have also presented the actual opportunities of prenatal diagnose, as well as the possibilities of termination of pregnancy. Generally speaking the low degree of risk eased our task.

We can finally state that the estimation of recurrence risk is only an aspect of the more wider activity of genetic counselling.

## CONCLUSIONS

In our study, as an argument for the genetic multifactorial inheritance, the familial distribution was certified in 9 cases (9%); we appreciate that this result is an underevaluation of the real data (some microforms could be lost) because the family inquiry wasn't realised directly by discussion with all relatives, but only with one parent.

A major objective of our study was the estimation of a correct recurrence risk to perform an accurate genetic counsel; for the majority of the studied cases (77%) the recurrence risk was considered small (2- 5%); only in 23% of cases the risk was considered medium (6-15%).

The proper genetic counselling was performed in accordance with all its general and specific rules of this complex and specialised medical act, but adapted to the needs imposed by the functional, aesthetic, psychological and social impact of labio-palatine clefts. The low degree of risk generally eased our counselling activity.

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