The most common genetic syndromes and associated anomalies in Latvian patients with cleft lip with or without palate

Baiba Lace, Biruta Barkane, Ilze Akota

SUMMARY

1 over 700 newborns every year is born with cleft lip with/or without palate, in 30% of cases there is a certain genetic mechanism underlying development of disease: chromosomal anomalies, monogenic diseases, exposure to teratogens or in utero disruptive mechanisms.

The objective of our study is to describe the most common genetic syndromes and associated anomalies in patients with CL/CP in Latvia.

Materials and methods

Study material was medical records obtained from Riga Cleft Lip and Palate Centre Registry in a time period of 1980 till 2005. There was analyzed information about patients with identified genetic syndromes and associated anomalies.

Results. In a time period from 1980 till 2005, the following genetic syndromes were identified: Van der Woude, Fetal alcohol syndrome, Holzgreve syndrome, Marfan syndrome, Myotonic dystrophy, Klippel-Feil syndrome, Patau syndrome, Potter sequence and Pierre Robin sequence. 16% of CL/CP patients have recognized genetic syndromes or associated anomalies, including profound, severe and moderate mental retardation. Number is lower than expected, but still correlates with date presented in other populations.

Conclusions. Long term follow-up of multidisciplinary specialists which includes cardiologists, clinical-geneticists and paediatricians, is needed for CL/CP patients with associated anomalies in order to identify timely side diseases and complications.

Key words: genetic syndromes, cleft lip with or without palate.

INTRODUCTION

Every year around the world more than 10 000 babies with cleft lip with or without cleft palate (CL/CP) are born with an average prevalence of 1 over 700 [1,2].

In 1942 physician P. Fogh-Andersen postulated, that inheritance had to play role in etiology of hare lip and cleft palate [3]. Studies of CL/CP revealed that in 70% of cases there is a complex inheritance based on genetic and environmental interaction. The other 30 % equally shares chromosomal abnormalities as a main reason of CL/CP, monogenic disorders, teratogenic effects, amniotic disruptions and unknown causes of CL/CP [1,4]. Up to date in Online Mandelian Inheritance of Man listed are more than 350 known monogenic disorders, where one of the symptoms is cleft lip with or without palate [5]. Considering these issues genetic counseling of patients with CL/CP appears to be very complex. In some patients recurrence risk calculation is based on empiric tables, which for different populations should be accordingly adapted. Associated anomalies in other patients could give us information about possible genetic mechanism underlying the disease, and increasing recurrence risk in families up to 50% or even more.

Frequencies of associated anomalies in patients with CL/CP are reported in a numerous publications and these numbers vary from a 3% to over 30%. In Stockholm survey 21% of patient had associated anomalies [6] of them 33% upper or lower limb malformations or the vertebral column, 24 % congenital heart disease. Hungarian epidemiologic analysis revealed 10% of associated anomalies in patients with CL/CP [7]. In a large population study in California 18% of patients with CL/CP had multiple congenital anomalies of unknown aetiology [7]. However RJ. Sprintzen concluded that associated anomalies occur in 63.4% of the sample and half of them were recognized syndromes [9].
The objective of our study is to describe the most common genetic syndromes and associated anomalies in patients with CL/CP in Latvia.

MATERIALS AND METHODS

Study material was obtained from Riga Cleft Lip and Palate Centre Registry in a time period of 1980 till 2005. Latvian CL/CP registry is localized in the Riga Cleft Lip and Palate Centre, which was established in 1964, and in the past years there had been cured more than 2470 patients with CL/CP. On an active account (visits yearly) there are more than 600 patients.

There was analyzed information about patients with identified genetic syndromes, cleft type, problems in anesthesia and family history of CL/CP patients. Presumably there is a number of unidentified genetic syndromes in Latvian CL/CP patients, therefore in analysis included date about associated anomalies, like congenital heart defects, CNS anomalies, upper and lower limb malformations and ocular anomalies.

The data collection was performed in accordance with the regulations issued by the Central Medical Ethics Committee of Latvia.

RESULTS

Identified genetic syndromes

55 (5%) patients with genetic syndromes were recognized in a time period from 1980 till 2005 from 1098 CL/CP patients. The following genetic syndromes were identified: Van der Woude, Fetal alcohol syndrome, Holzgreve syndrome, Marfan syndrome, Myotonic dystrophy, Klippel – Feil syndrome, Patau syndrome, Potter sequence and Pierre Robin sequence (Table 1).

Patients with Patau syndrome usually are not referred to Riga Cleft Lip and Palate Centre and subsequently not included in registry, due to the severity of multiple congenital anomalies.

Associated anomalies in non-syndromic CL/CP patients

69 (6%) of 1043 non-syndromic CL/CP patients have associated anomalies. 23 (33%) non-syndromic CL/CP patients have upper or lower limb malformations, 33 (48%) CL/CP patients have cardiovascular system malformations, 5 (7%) patients have ocular defects and 8 (12%) patients have CNS malformations.

Profound, severe or moderate mental retardation is reported in 57 (5%) non-syndromic CL/CP patients.

Cleft type

In CL/CP patients (n=1098), CL is observed in 19.8% of cases, CP (cleft palate) is observed in 34.2% of cases and CLP (cleft lip and palate) is observed in 46.0% of cases.

Only 4% of patients with identified genetic syndromes have CL and CLP. Rests of the patients (96%) have CP. Severe form of cleft was reported in 50% of CP patients with genetic syndromes.

Positive family history

12.5% of syndromic CL/CP patients have affected 1st degree relatives (mothers and sibs).

Table 1. Identified genetic syndromes, sequences and chromosomal aberrations.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Number of affected patients</th>
<th>Male:female ratio</th>
<th>CL/CLP type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal rearrangements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td>1</td>
<td>-</td>
<td>Complete CLP</td>
</tr>
<tr>
<td>Patau syndrome</td>
<td>1</td>
<td>-</td>
<td>Complete CLP</td>
</tr>
<tr>
<td>22qdel</td>
<td>1</td>
<td>-</td>
<td>Cleft Palate (CP)</td>
</tr>
<tr>
<td>Exposure to teratogens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>4</td>
<td>1:1</td>
<td>CP</td>
</tr>
<tr>
<td>Mendelian syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Woude syndrome</td>
<td>12</td>
<td>1:1</td>
<td>41% Complete CLP, 50% CP, 9% CL and cleft soft palate CP</td>
</tr>
<tr>
<td>Potter syndrome</td>
<td>1</td>
<td>-</td>
<td>CP</td>
</tr>
<tr>
<td>Klippel-Feil syndrome</td>
<td>1</td>
<td>-</td>
<td>CP</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1</td>
<td>-</td>
<td>Velopharyngeal insufficiency CP</td>
</tr>
<tr>
<td>Dystrophia myotonica</td>
<td>1</td>
<td>-</td>
<td>CP</td>
</tr>
<tr>
<td>Pierre Robin sequence</td>
<td>32</td>
<td>1:1.9</td>
<td>CP/CLP</td>
</tr>
</tbody>
</table>

Problems in anesthesia

There were no problems related to anesthesia in syndromic CL/CP patients.

DISCUSSION

Low percentage (16%) of syndromic and non-syndromic CL/CP patients with associated anomalies is lower than expected, but still correlates with date presented earlier in other populations; presumably, explanation mostly lies in the selection of patients. Cleft centre registry does not contain information about all patients born with a cleft, like newborns with severe multiple congenital anomalies. An autopsy date also is not included in registry.

Syndromic CL/CP patients mostly have cleft palate, cleft lip and palate was observed only in a few cases. Two times higher frequency of cleft palate in syndromic CL/CP patients indicates different aetiology of it in comparison with cleft lip with or without palate, which is in accordance of published date [9].

Cleft palate in syndromic CL/CP patients is observed in severe form in 50% of cases, which requires additional procedures of plastic surgery and orthodontic therapy for the satisfying results.
Positive family history of syndromic CL/CP patients was observed in 12.5% of cases, therefore it was concluded, that most of the cases are sporadic and unpredictable, thus complicating genetic counselling.

Hypothesis was built, that syndromic CL/CP patients would have more problems during anaesthesia due to the congenital defects of other organ systems. Results showed that syndromic CL/CP patients did not have any difficulty in anaesthesia.

The most frequent genetic syndromes in CL/CP patients

Pierre Robin sequence is one of the most common syndromes in patients with CL/CP worldwide; it is characterized by three features, micrognathia, glossoptosis and cleft palate, due to underdevelopment of the lower jaw (Figure 1). Difficulties in genetic counselling of patients with Pierre Robin sequence are related to a number of genetic syndromes, where Pierre Robin sequence is a part of clinical symptoms, like, Stickler syndrome, Catel-Menzke, Fetal alcohol syndrome or del22q syndrome. Pierre Robin sequence could be the only presentation of Stickler syndrome in childhood, myopia usually develops later in life, therefore yearly follow-ups for all Pierre Robin sequence patients until 16 years would be advisable.

Van der Woude syndrome (VWS) is a recognizable through typical pits or/and sinuses on a lower lip and cleft palate (Figure 2). VWS1 is the most common cleft syndrome and genetic background had been discovered. S. Kondo et al. [9] identified mutations in the IRF6 gene, which causes Van der Woude syndrome.

Two of twelfth CL/CP patients have an oral synechias, but 4 of 12 have mental retardation at various degrees, which is unusual finding in patients with Van der Woude syndrome. Genetic counselling for Van der Woude patients is recommended, because it has autosomal dominant mode of inheritance and 50% recurrence risk for offspring. Van der Woude syndrome has variable expressivity; therefore careful examination of parents is important.

Number of patients with Fetal alcohol syndrome (FAS) in Latvia unfortunately does not have a tendency to decrease in past years. Patients with FAS is characterized by microcephaly, mild to severe mental retardation, growth deficiency, minor anomalies, such as thin upper lip and flat filtrum, occasionally congenital heart disease (Figure 3). Future prognosis of these patients depends of the mental retardation degree and presence of congenital heart disease.

CONCLUSIONS

Clinical management of patients with CL/CP is very complicated due to the several factors. Surgical correction, orthodontic and speech therapy could require a number of procedures and intensive work to reach good results for syndromic CL/CP patients. Individual approach and long term follow-up of multidisciplinary specialists for each syndromic CL/CP patient is necessary in order to identify early upcoming complications or side diseases.

The reported frequency of associated anomalies and genetic syndromes has implications for the genetic counselling at cleft centres. Numbers of associated anomalies in CL/CP patients justify Cleft centre work organization as a team work, which includes specialists from different areas, like cardiologists, ophthalmologists, clinical-geneticists and paediatricians.

ACKNOWLEDGMENTS

We would like to thank families, who agreed to participate in study. This study was realised within a framework of Baltic–Taiwan joint research project.

REFERENCES


Received: 19 02 2006
Accepted for publishing: 27 06 2006