Orofacial clefts associated with cardiac anomalies: 27 years of experience of a multidisciplinary group in a tertiary hospital in Portugal

Fendas orofaciais associadas a anomalias cardíacas: 27 anos de experiência de um grupo multidisciplinar em um hospital terciário em Portugal

Abstract

AIMS: Orofacial clefts (OFC) are a heterogeneous group of birth defects arising in about 1.7/1000 newborns. They can occur with other congenital anomalies, including heart defects. We aim to describe a population with orofacial clefts and associated cardiac anomalies.

METHODS: Retrospective study of patients attended in the Cleft Lip and Palate Multidisciplinary Group outpatient clinic at Hospital Universitario São João, Porto-Portugal. Medical records from January 1992 through December 2018 were reviewed. Patients were divided into four groups according to the Spina classification: cleft lip (CL), cleft lip and palate (CLP), isolated cleft palate (CP) and atypical cleft (AC). Further categorization included gender, affected relatives, associated congenital anomalies and syndromes.

RESULTS: From the 588 patients included, 77 (13%) presented cardiac anomalies. Of those with orofacial cleft and cardiac anomalies, 53% were males and 17% had known affected relatives. CP was the most common cleft among patients with cardiac anomaly (~56%). Additional congenital anomalies were found in 89.7% of patients, namely facial defects, central nervous system, renal and skeletal malformations. A recognizable syndrome was identified in 61.5%, being Pierre-Robin the most common (n=22), followed by 22q11.2 microdeletion (n=9). Both additional congenital anomalies and recognizable syndromes were significantly more prevalent in patients with heart disease (p<0.05). The main groups of cardiac anomalies were left-to-right shunt (n=47) and right ventricular outflow tract obstruction (n=14). From these, 26 had a ventricular septal defect, 15 atrial septal defect and seven patients had tetralogy of Fallot. Five patients had dysrhythmias.

CONCLUSIONS: Due to the high prevalence of cardiac anomalies in the cleft population, a routine cardiac evaluation should be performed in all these patients.

KEY-WORDS: Cleft lip, cleft palate, congenital abnormalities, congenital heart defect.

Resumo

INTRODUÇÃO: As fendas lábio-palatinas são um grupo heterogêneo de defeitos congênitos que ocorrem em cerca de 1,7 / 1000 recém-nascidos. Eles podem ocorrer com outras anomalias congênitas, incluindo defeitos cardíacos. O nosso objetivo é descrever uma população com fendas lábio-palatinas e anomalias cardíacas associadas.

MÉTODOS: Estudo retrospectivo de doentes seguidos pelo Grupo Multidisciplinar de Fendas Lábio-Palatinas no Hospital Universitário São João, Porto-Portugal. Foram analisados os prontuários médicos de janeiro de 1992 a dezembro de 2018. Os doentes foram divididos em quatro grupos, de acordo com a classificação de Spina: fenda labial (CL), fenda labial e palatina (CLP), fenda palatina isolada (PC) e fenda atípica (CA). Outras categorizações incluíram sexo, parentes afetados, anomalias e síndromes congênitas associadas.

1 Centro Hospitalar e Universitário de São João (CHUSJ), Porto, Portugal.
RESULTADOS: Dos 588 pacientes incluídos, 77 (13%) apresentaram anomalias cardíacas. Daqueles com fenda e anomalias cardíacas, 53% eram do sexo masculino e 17% tinham parentes afetados. A PC foi a fenda mais comum entre os doentes com anomalia cardíaca (aproximadamente 56%). Anomalias congénitas adicionais, como defeitos faciais, malformações do sistema nervoso central, renais e esqueléticas foram encontradas em 89,7%. Síndromes foram identificadas em 61,5%, sendo Pierre-Robin a mais comum (n = 22), seguida pela microdeleção 22q11.2 (n = 9). Anomalias congénitas adicionais e a presença de uma síndrome genética foram significativamente mais prevalentes em doentes com doença cardíaca associada (p <0,05). Os principais grupos de anomalias cardíacas foram shunt da esquerda para a direita (n = 47) e obstrução da via de saída do ventrículo direito (n = 14). Destes, 26 apresentaram comunicação interventricular, 15 comunicação interauricular e sete pacientes apresentaram tetralogia de Fallot. Cinco pacientes apresentaram disritmias.

CONCLUSÕES: Devido à elevada prevalência de anomalias cardíacas na população de doentes com Fenda Labial-Palatina, aconselhamos uma avaliação cardíaca de rotina em todos.

PALAVRAS-CHAVE: Fenda labial, fenda palatina, anomalias congénitas, cardiopatia congénita.

ABBREVIATIONS: AC: atypical cleft; ASD, atrial septal defect; CHD, congenital heart diseases; CL, cleft lip; CL/CLP, cleft lip with or without cleft palate; CLP, cleft lip and palate; CP, cleft palate; OFC: orofacial cleft; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

INTRODUCTION

Orofacial clefts (OFC) are a group of congenital defects that include cleft lip with or without cleft palate (CL/CP) and cleft palate (CP) (1). It is estimated that 1 to 2/10,000 live births have OFC (2). This group of malformations is the second leading cause of congenital anomalies in live births (1). OFC classification is complex and phenotypically diverse (3). According to the Spina classification, 1972, OFC may be classified according to its anatomical location (4).

In 30% of cases, OFC are associated with other congenital defects and are part of a genetic syndrome. Non-syndromic OFC have a multifactorial origin, combining genetic and environmental factors. Several studies have been conducted to expand knowledge of the etiology of isolated OFC (5). The prevalence of syndromic OFC varies worldwide, ranging, according to the literature, between 1.5% and 63% (6). Among the reported congenital abnormalities were described skeletal system disorders, central nervous system disorders, congenital heart defect (CHD), respiratory system abnormalities, polydactyly, eyes and ear anomalies, limb anomalies, chromosomal disorders, talipes equinovarus, CLP, anencephaly, spina bifida, and many more (7).

Available data present cardiovascular malformations as one of the most common congenital defects in CLP patients. Furthermore, congenital heart disease is more prevalent in OFC children than in the general pediatric population (5-15%) (8, 9). These cardiovascular conditions included: atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), tetralogy of Fallot, truncus arteriosus, transposition of the great vessels, aortic stenosis and pulmonary stenosis. Patent foramen oval was not included because is considered an anatomical variation and not a cardiac malformation (10, 11).

The study of the association between OFC and other congenital defects is of major importance, helping to provide the appropriate multidisciplinary management and to improve prognosis too. Taking the previous into account, we aim to describe our population of OFC with associated CHD (12).

Methods

A retrospective study of patients that attended the Cleft Lip and Palate Multidisciplinary Group at Centro Hospitalar Universitário São João, Porto, Portugal, for 27 years, was performed. Medical records from January-1992 through to December-2018 were reviewed. The study was approved by Ethics Committee of Centro Hospitalar São João, Faculty of Medicine, University of Porto.

The birth rate of the metropolitan area of Porto ranged between 13% and 8.4% in the study period, with an estimated prevalence of congenital heart defects of 79,17/10,000 births and 12,26 / 10,000 births of orofacial clefts. National prevalence of congenital defects is 259.76/ 10,000 births.

In the northern region of the country the Centro Hospitalar Universitário São João is the only reference center, so that all patients from both the public and private network are followed in our Unit.

Patients were divided into four groups, according to the Spina classification (4): cleft lip...
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From all 588 patients, the patients with associated CHD, were then grouped according to their pathophysiology into 1) left-right shunt (ASD, VSD, PDA); 2) left ventricular outflow tract obstruction; 3) right ventricular outflow tract obstruction; 4) parallel circulation (transposition of the great vessels); 5) dysrhythmias; 6) other cardiac conditions; 7) combined cardiac defects (two or more).

All patients were followed-up in a multidisciplinary group, which included pediatrics, cardiology, otorhinolaryngology, genetics, pediatric surgery, orthodontics and speech therapy.

The analysis was performed using IBM SPSS Statistics 21. The chi-square test was applied to study the association between CHD and the occurrence of additional congenital anomalies in OFC (significant if the p value below 0.05).

**Results:**

There was a total of 588 patients, 338 (57.4%) were males. Associated congenital anomalies were found in 247 (43.5%) patients: of that 342 (58.2 %) were males.

Among patients with OFC, a syndrome was identified in 284 (48.3%) patients, family history was positive in 176 (30.1%) and 176 (29.9%) had a prenatal diagnosis The other systems more frequently associated with the orofacial clefts were facial, cardiovascular, and musculoskeletal, followed by central nervous system.

Seventy-seven (13%) patients presented CHD, 40 (52%) of whom were males and 13 (17%) had known affected relatives. According to the Spina classification, 43 (65.8%) had CP, 20 (26.0%) had CLP, 11 (14.3%) had CL and 3 (3.9%) had AC.

CP was the most common cleft among patients with cardiac anomalies 43 (55.8%). Additional congenital anomalies were found in 69 (89.7%) of these patients, being the facial defects, central nervous system, renal and skeletal malformations the most common. A recognizable syndrome was identified in 47 (61.0%) and the most commonly found were Pierre-Robin (n=22), 22q11.2 microdeletion (n=9) and Goldenhar (n=3). Both, additional congenital anomalies, and recognizable syndromes were significantly more common in patients with CHD (p<0.05).

The main groups of cardiac anomalies were left-to-right shunt (n=47) and right ventricular outflow tract obstruction (n=14). VSD and ASD were the most prevalent diagnosis (33.8% and 19.4% respectively. See on Table 1).

**TABLE 1 –** Descriptive of cardiac conditions associated with OFC patients, according to main groups of classification.

| Cardiac defect                        | n (%) |
|---------------------------------------|-------|
| **Left-right shunt**                  |       |
| ASD                                   | 15 (19.4) |
| VSD                                   | 26 (33.8) |
| PDA                                   | 6 (7.8) |
| **Right ventricular outflow tract obstruction** | 14 (18.2) |
| Tetralogy of Fallot                   | 7 (9.1) |
| Pulmonary stenosis                    | 6 (7.8) |
| Pulmonary atresia                     | 1 (1.3) |
| **Left ventricular outflow tract obstruction** | 9 (11.7) |
| Aortic stenosis                       | 1 (1.3) |
| Bicuspid aortic valve                 | 4 (5.2) |
| Aortic atresia                        | 1 (1.3) |
| Aortic dilatation                     | 1 (1.3) |
| Coarctation of aorta                  | 2 (2.6) |
| **Other cardiac pathologies**         | 7 (9.1) |
| Dilated miocardiopathy                | 1 (1.3) |
| Hypertrophic miocardiopathy           | 1 (1.3) |
| Truncus arteriosus                    | 2 (2.6) |
| Single ventricle physiology           | 1 (1.3) |
| Dextrocardia                          | 1 (1.3) |
| Levocardia                            | 1 (1.3) |
| **Total**                             | 77 (100) |

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
Seven patients presented other cardiac conditions, namely truncus arteriosus – (2.6%) (Table 1).

Five patients had dysrythmias, three of them associated with structural cardiac anomalies. Eleven patients (14.3%) combined two or more cardiac conditions. The most frequent one was the association of bicuspid aortic valve and VSD.

**Discussion:**

Clefts and craniofacial malformations are commonly seen around the world, considered by the WHO as a public health problem, requiring a multidisciplinary approach due to its frequent association with other organic abnormalities. This was the highlight of this study: to claim attention to the not rare association of these malformations, which carry important comorbidities and a relevant impact on patient's lives.

In our study, we found a higher frequency of male patients, which may possibly be in agreement with other international studies that established a higher risk of OFC in men (5, 9, 11). According to the type of OFC distribution, more than half of the patients had CP, as reported in other studies (3, 9). CLP and CL alone are typically more common in boys and CP is traditionally more prevalent among girls, with a boy to girl ratio of 1.6: 1 for CLP, 1.2: 1 for CL and 0.9: 1 for CP (18).

However, several studies reported other prevalence rates, which shows that there isn’t an established relation between OFC type and associated comorbidities. These differences may also be explained by different target populations, different methods and objectives around worldwide studies.

It is important to reinforce the association with other organic malformations and also genetic syndromes in about 90% (p<0.05). The syndromes most implied in our study overlap with international data about this issue. An attempt diagnosis is essential for adequate follow-up and genetic counseling, including prenatal appointments (13).

We found an important prevalence of cardiac anomalies in OFC patients (23%), similar to the existing studies (14). However, the prevalence is higher than published in countries like Brazil or England (11, 15).

The most frequent cardiac pathology found was left-right shunts (58%), more specifically ASD and VSD, which is in accordance with other results (14, 16, 17). We must be aware of the high percentage of combined cardiac defects, which may reflect a higher complexity in the approach of OFC patients.

One of the limitations of our study is the absence of risk factors for cardiac congenital anomalies, which may include smoking, alcoholism, obesity, arterial hypertension, dyslipidemia, and diabetes mellitus during pregnancy. Another important limitation of our study is the lack of characterization of possible gender differences between the general prevalence of OFC and also the respective subtypes.

Other risk factors for malformations such as maternal diseases, intercurrences during pregnancy and consanguinity should also be studied. Future studies should clarify these determinants in OFC patients and improve the prevention of CHD in these patients. The correlation between risk factors and the occurrence of cardiac pathology is not clear at the moment. As far as we know, there is no biomarker of the coexistence of cardiac defects and OFC in non-genetic cases. The association between OFC and cardiac defects may be explained by embryogenesis. Neural crest cells influence the development of craniofacial and cardiac tissues and contribute to conotruncal endocardial cushions which separate the outflow tract of the heart into pulmonary and aortic channels (19). Folate deficiency may also contribute to these anomalies. The association between folate supplementation and CHD has been confirmed by several studies, though experimental evidence is still lacking. However, folate supplementation before and during first pregnancy trimester is highly recommended. Although in Portugal folate supplementation during pregnancy is now routinely implemented and folate deficiency is not a prevalent comorbidity, it may be valuable to study this possible association in the near future (20).

The important prevalence of the cardiac disease in OFC patients, associated with the complexity and the potential risk of cardiac defects, justify by itself a routine evaluation by Cardiology as part of the multidisciplinary
medical approach to these patients (21). Based on our results, we suggest an extension of cardiac evaluation, including electrocardiogram and echocardiogram, performed routinely by Pediatric Cardiology in all OFC patients. Moreover, this evaluation should be extended to prenatal life. Every time an OFC is suspected during pregnancy, a fetal echocardiogram should be performed, aiming to get a “full picture” of the problem and, in that way, allowing to achieve a timely and correct approach to the patient and his family.

In our center, the multidisciplinary approach and the follow-up are performed throughout many years, sometimes into adulthood, focusing on the individualization of medical care, which includes sometimes multiple surgeries and long-term treatments. We believe that the long course follow-up is crucial to improve the prognosis of these patients.

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The authors declare no competing interests relevant to the content of this study.

**Authors’ contributions.**

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

**Availability of data and responsibility for the results**

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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Vanessa Oliveira Gorito:
Resident of Pediatrics, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP), PhD student at Instituto de Saúde Pública da Universidade do Porto (ISPUP), Portugal.

Marta Isabel Pinheiro:
Resident of Pediatrics, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP), Portugal.

Cristina Ferreras:
Resident of Pediatrics, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP).

Marisa Pereira:
Resident of Pediatric Cardiology, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP), Portugal.

Sofia Granja:
Hospital Assistant of Pediatric Cardiology, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP), Portugal.

Ana Maria Maia:
Graduated Hospitalar Assistant of Pediatrics, Centro Hospitalar e Universitário de São João (CHUSJ); Invited Assistant at Faculdade Medicina Universidade do Porto (FMUP), Chief of Pediatric External Consultation at Centro Hospitalar e Universitário de São João (CHUSJ); Team Leader at Emergency Service at Centro Hospitalar e Universitário de São João (CHUSJ), Portugal.

Mailing address:
Vanessa Alexandra Oliveira Gorito
Centro Hospitalar e Universitário de São João.
Alameda Prof. Hernâni Monteiro, 4200-319
Porto, Portugal.