Special Article

Prevalence of Congenital Heart Diseases in Patients with Orofacial Clefts: A Systematic Review

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Background: *The reports on prevalence rates of congenital heart diseases (CHDs) in patients with orofacial clefts (OFCs) have varied widely.*
Objective: *To systematically review the prevalence rates of CHDs in patients with OFCs.*
Material and Method: *A computer search was conducted through the PubMed from 1950 to June 2015 using key words or search terms of congenital heart diseases, orofacial clefts, cleft lip/palate and prevalence.*
Results: *The search resulted in nine studies with 598 CHDs cases identified in 5,707 patients with OFCs. The prevalence of CHDs in patients with OFCs ranged from 3.9% to 23.9%. The five prospective studies had prevalence rates of 12.0% (95% confidence interval [CI]: 10.9 to 13.2) whilst the four retrospective studies had prevalence rates of 8.6% (95% CI: 7.5 to 9.8). Concerning the prospective studies, the newborn study had a higher prevalence than those of other childhood studies [23.9% vs. 11.5% (95% CI: 10.4 to 12.7)]. The newborn study with the use of echocardiography had a higher prevalence than those without using echocardiography (23.9% vs. 12.8%). Atrial septal defect was the most frequent CHD found.*
Conclusion: *CHD is commonly found in a patient with OFC. Echocardiography should be used to assess CHD in patients with OFCs.*

Keywords: *Congenital heart diseases, Orofacial clefts, Cleft lip, Cleft lip and palate, Cleft palate, Prevalence, Incidence*

J Med Assoc Thai 2015; 98 (Suppl. 7): S22-S27
Full text. e-Journal: *http://www.jmatonline.com*

Orofacial clefts (OFCs), including cleft lip (CL) or cleft lip with cleft palate (CLP) and isolated cleft palate (CP), are common birth defects of the head and neck and have complex etiologies with environmental and genetic backgrounds[1,2]. The OFCs prevalence has been estimated to be around one in 700 live births[1,2]. In addition to isolated occurrence, OFCs can have other congenital associated malformations and recognized syndromes[1,2]. A congenital heart disease (CHD) was the most common associated malformation, but there were wide variations in the prevalence rates of CHDs in patients with OFCs in a range of 1.3% to 27.0% according to previous reports[3-16]. Importantly, CHD was reported as the principal cause of death among infants with OFCs[17].

There is a need to have reliable data about the prevalence of CHDs in patients with OFCs because this may guide to better understanding of its malformation process. Moreover, a precise care could be better planned. Although knowledge on the coexistence of CHD and OFCs is crucial, few studies have addressed this issue.

The aim of this study was to systematically review the prevalence of CHDs occurring in patients with OFCs.

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Material and Method

Data source and search strategy

A systematic literature search was conducted through electronic databases in the PubMed for all publications from 1950 to June 2015 using search strategy with key words or search terms including congenital heart disease AND orofacial clefts OR cleft lip palate AND prevalence OR incidence. The search results of relevant papers in all languages were included and screened. The titles and abstracts of the 1968 relevant papers were screened independently by two

authors (VP and MP) to identify potentially relevant papers for which full text publications were retrieved. Reference lists of included articles were screened for additional relevant articles that may have been missed in the database search.

Definitions

CHD was defined as a defect in the structure of the heart or great vessels that was present at birth. OFC included cleft lip or cleft lip with cleft palate and isolated cleft palate.

The study selection

All identified published prospective and retrospective studies of the prevalence rates of CHDs in patients with OFCs were considered for inclusion in this review.

The authors excluded the followings: studies limited only to clinical features and cleft patterns without a mention of the prevalence of CHD.

When a study was eligible for inclusion, two authors (VP and MP) verified the paper.

Data extraction and quality assessment

Using a standardized data extraction form, data on study design, study setting, country, age and number of patients included, types of CHD, and types of OFC were extracted. Studies were assessed on completeness of data and origin of the data.

Statistical analysis

The prevalence of CHD in patient with OFC was presented with average values (95% confidence interval).

Results

The title and abstract search initially identified 1,968 articles. A thorough evaluation of these titles and abstracts led to the exclusion of the 1,956 articles that were unrelated to the prevalence rates of CHDs in patients with OFCs. Of the 12 papers remained after title and abstract screening, the full text review revealed 8 papers containing relevant data. There was one additional article after reference checking was performed. This additional paper was not initially retrieved by the original search because it was not indexed in the searched database. Thus, nine papers were eligible for the inclusion into this systematic review (Fig. 1).

This systematic review resulted in nine studies which CHDs identified in 598 patients in the population

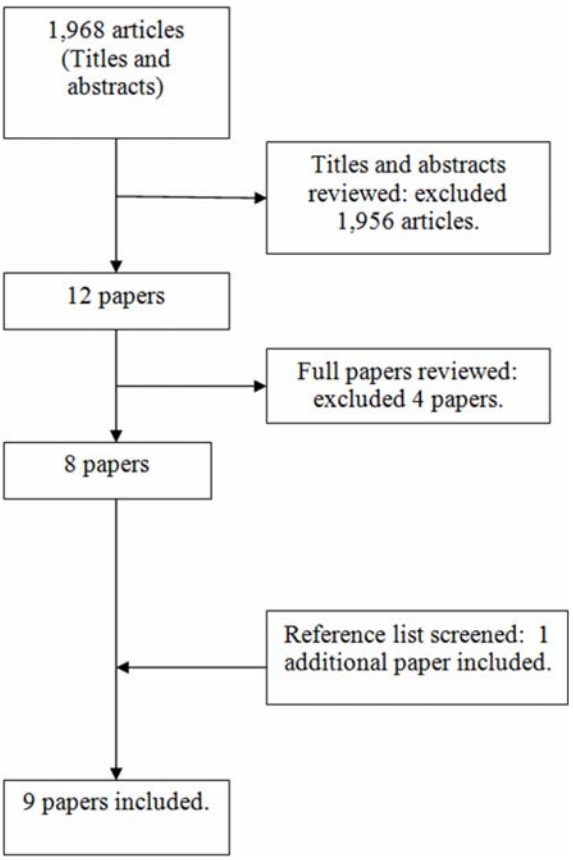

Fig. 1 Flow diagram of paper search and papers included into this systematic review.

of 5,707 patients with OFCs. There were five reports of prospective studies and four reports of retrospective studies[3-11]. The prevalence of CHD in patients with OFCs ranged from 3.9% to 23.9%[3-11]. The five prospective studies had prevalence rates of 12.0% (95% confidence interval [CI]: 10.9 to 13.2)[3-7] whilst the four retrospective studies had prevalence rates of 8.6% (95% CI: 7.5 to 9.8)[8-11]. Concerning the prospective studies, the newborn study had a higher prevalence than those of other childhood studies [23.9% vs. 11.5% (95% CI: 10.4 to 12.7)][3-7]. The newborn study with the use of echocardiography had a higher prevalence than those without using echocardiography (23.9% vs. 12.8%)[4,8]. CHDs found were more frequent in patients with CP than CL or CLP[3,4,8-10] (Table 1). The patients with syndrome had higher prevalence of CHD than patients with non-syndromic OFCs[6].

For the CHD found in patients with OFCs, atrial septal defect (ASD) was the most frequent[3-6,8-11] and the second common was ventricular septal defect

(VSD)[7].

The three major CHDs in patients with OFCs according to the prevalence rates were ASD, VSD and PDA[3-11].

Discussion

This systematic review presented the high prevalence of CHD in patients with OFCs in a range of 3.9-23.9%[3-11]. The present review confirmed previous studies that the prevalence of CHD and associated malformations is highly associated with isolated cleft palate than cleft lip alone or cleft lip with cleft palate[3,8,9]. Prospective studies of the occurrence of CHD in patients with OFCs showed higher prevalence rates than the retrospective studies[3-11]. Concerning the prospective studies, the newborn study showed a higher prevalence rate than other childhood prospective studies[3-7]. The newborn study with the use of echocardiography had a higher prevalence than those without using echocardiography (23.9% vs. 12.8%)[4,8]. For the CHD found in patients with OFCs, atrial septal defect (ASD) was the most frequent and the second common CHD was ventricular septal defect (VSD).

The variations in the prevalence of CHD in patients with OFCs varied widely due in part to differences in study types and patient selection processes[3-11]. The present study documented higher prevalence rates of prospective studies than those from retrospective studies[3-11] (Table 1). However, the prevalence rates can be varied even among the same type of studies, depending on the age of the studied population. Some mild form of CHDs such as small VSD, ASD or PDA may undergo spontaneous closure and disappear later in childhood[18]. In contrast, some severe forms of CHDs may cause patients died in early life. In this study, the newborn studies had the highest prevalence rate of the CHD and was higher than other childhood prevalence reported. The differences in the method used to diagnose CHD can be a cause of variations in the prevalence of CHD. There were five studies used echocardiography as a screening tool and the prevalence rates of CHD of these studies were relatively higher than those using routine diagnostic tools such as physical examination, chest x-ray and electrocardiography[3-11].

This study has confirmed the fact that CHD is one of the most common associated malformations observed in infants and children with OFCs. However, our results showed that infants and children with OFCs had a higher prevalence of CHD than those without OFCs for whom the CHD birth prevalence is about 1%[3-11]. It is possible that CHDs and OFCs are frequently seen together as a result of the intertwined embryological development of the heart and orofacial area. From this study, atrial septal defect (ASD) was the most frequent and the second common was ventricular septal defect (VSD) found in association with the OFCs. The molecular mechanism underlying highly prevalent ASD and VSD have remained elusively. Small ubiquitin-like modifier (SUMO-1) is needed for normal cardiac development in mice and SUMO-1 is essential for the prevention of OFCs in human. Animal study demonstrated that SUMO-1 knockout mice developed ASD and VSD. Thus, diminished sumoylation activity whether by genetics, environmental toxins and/or drugs may contribute to susceptibility to the induction of both CHD and OFC[19].

Conclusion

The prevalence of CHD in patients with OFC was higher in the prospective studies and with the use of echocardiography as the diagnostic tool. ASD and VSD were the most common CHD found in patients with OFCs. Echocardiography should be a diagnostic tool to assess CHD in patients with OFCs.

What is already known on this topic?

A high prevalence of CHD is found in patients with OFCs.

What this study adds?

ASD and VSD are the most common CHD found in patients with OFCs. Echocardiography can add up more undiagnosed CHD in patients with OFCs.

Acknowledgement

The authors wish to thank the Center of Cleft Lip-Cleft Palate and Craniofacial Deformities, Khon Kaen University in association with "Tawanchai Project" for its support.

Potential conflicts of interest

None.

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Table 1. A summary of documented prevalence rates on congenital heart disease in patients with orofacial clefts

Authors/ year	Sample size/ location/setting	Mean age in month ± SD (range)	Associated malformation (%)	Associated syndrome (%)	CHD/CL (%)	CHD/CLP (%)	CHD/CP (%)	CHD/OFC (%)	The most common CHD (% of all CHD)
Sun T et al, 2013[3] (P) [+]	2,180[+] China/ Hospital	33.2±31.3 (2-144)	657[+] (30.1)	NA[+]	32/755[+] (4.2)	120/738[+] (16.3)	144/687[+] (20.9)	296/2,180[+] (13.6)	ASD* (39.7)
Altunhan et al, 2012[4] (P)	121/Turkey/ Hospital	Newborn	80 (66.1)	31 (25.6)	54/86 (62.8)		26/35 (74.3)	29/121 (23.9)	ASD* (NA)
Shafi et al, 2003[5] (P)	123/Pakistan/ Hospital	NA (Children)	35 (28.4)	34 (27.6)	NA	NA	NA	18/123 (14.6)	ASD* (38.9)
Barbosa et al, 2003[6] (P)	220/Brazil/ Referral center	112±101 (1-575)	28 (12.7)	28 (12.7)	NA	NA	NA	21/220 (9.5)	ASD* (28.6)
Milerad et al, 1997[7] (P)	616/Sweden/ Referral center	NA (Children)	127 (20.6)	33 (5.4)	NA	NA	NA	23/583[+] (3.9)	VSD (30.4)
Lee et al, 2015[8] (R)	980/Korea/ Survey	Newborn	449 (45.8)	31 (3.2)	14/245 (5.7)	30/243 (12.3)	81/492 (16.5)	125/980 (12.8)	ASD (45.4)
Pradubwong et al, 2014[9] (R)	123/Thailand/ Referral center	NA (1-60)	17 (13.8)	5 (4.1)	0/30 (0)	5/74 (6.8)	2/19 (10.5)	7/123 (5.7)	ASD* (28.6)
Rawashdeh et al, 2008[10] (R)	196/Jordan/ Referral center	128±105 (3-550)	28 (14.3)	NA	9/162 (5.6)		8/34 (23.5)	17/196 (8.7)	ASD (41.2)
Liang et al, 1999[11] (R)	1148/Taiwan/ Survey	NA (Children)	NA	NA	NA	NA	NA	62/1148 (5.4)	ASD (23.0)

Number presented = number of patients; P = indicates prospective study; R = retrospective study; SD = standard deviation; CHD = congenital heart disease; CL = cleft lip; CLP = cleft lip and palate; CP = cleft palate; OFC = orofacial clefts; ASD = atrial septal defect; NA = not available; VSD = ventricular septal defect

* with the use of Echocardiography, [+] All study populations were non-syndromic OFCs,

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ความชุกของโรคหัวใจพิการแต่กำเนิดในผู้ป่วยปากแหว่งเพดานโหว่: การศึกษาทบทวนอย่างเป็นระบบ

วิภาวี ปะนะมณฑา, สุธีรา ประดับวงษ์, มนัส ปะนะมณฑา, บวรศิลป์ เขาวน์ชื่น

ภูมิหลัง: *ความชุกของโรคหัวใจพิการแต่กำเนิด (CHD) ในผู้ป่วยปากแหว่งเพดานโหว่ (OFC) ยังไม่มีการศึกษาอย่างเป็นระบบ*

วัตถุประสงค์: *เพื่อศึกษาความชุกของ CHD ในผู้ป่วย OFC*

วัสดุและวิธีการ: *ศึกษาความชุกของ CHD ในผู้ป่วย OFC จากรายงานในฐานข้อมูล Pubmed ตั้งแต่ปี พ.ศ. 2493 ถึง มิถุนายน พ.ศ. 2558*

ผลการศึกษา: *จากรายงาน 9 เรื่อง มีผู้ป่วย CHD จำนวน 598 รายในผู้ป่วย OFC จำนวน 5,707 ราย ความชุกของ CHD ในผู้ป่วย OFC พบตั้งแต่ร้อยละ 3.9 ถึง 23.9 การศึกษาแบบ prospective 5 รายงาน พบความชุกร้อยละ 12.0 (95% confidence interval [CI]: 10.9 to 13.2) สูงกว่าการศึกษาแบบ retrospective 4 รายงาน ซึ่งพบความชุก 8.6% (95% CI: 7.5 to 9.8) และในการศึกษาแบบ prospective study ที่ศึกษาในเด็กแรกเกิดพบความชุก (23.9%) สูงกว่าการศึกษาในเด็กโต [23.9% vs. 11.5% (95% CI: 10.4 to 12.7)] การตรวจหัวใจโดยใช้คลื่นเสียงสะท้อนหัวใจจะได้อัตราความชุกของ CHD สูงขึ้นเมื่อเทียบกับการตรวจที่ไม่ได้ใช้คลื่นเสียงสะท้อนหัวใจ (23.9% vs. 12.8%) โรครูรั่วของผนังหัวใจห้องบน (ASD) พบได้บ่อยที่สุด*

สรุป: *CHD พบได้บ่อยในผู้ป่วย OFC ควรใช้คลื่นเสียงสะท้อนหัวใจตรวจประเมินหัวใจในผู้ป่วยปากแหว่งเพดานโหว่*