Special Article

Cardiovascular Malformations in Patients with Oculo-Auriculo-Vertebral Spectrum: A Systematic Review

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Background: *Reported frequency and type of cardiovascular malformations in patients with Oculo-Auriculo-Vertebral Spectrum (OAVS) are documented to vary; however, a systematic review of these studies is lacking.*
Objective: *To systematically review the frequency and type of cardiovascular malformations in patients with OAVS.*
Material and Method: *A systematic literature search was conducted through PubMed and Scopus between 1952 and June 2017 using search terms of cardiovascular malformations or congenital heart diseases and oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum].*
Results: *Of the 22 studies included, there were 348 (21%; range, 1 to 58%) patients with cardiovascular malformations found in a study population of 1,685 (range, 7 to 294) cases of OAVS. The patients, who had cardiovascular malformations, also had higher frequencies of either vertebral anomalies or associated extra-craniofacial abnormalities in other organ systems. In the large population based studies, the conotruncal heart diseases (cardiac defects in the outflow parts of the heart, i.e., tetralogy of Fallot or truncus arteriosus) were significantly associated with OAVS.*
Conclusion: *Cardiovascular malformations occur commonly in patients with OAVS and some patients may be related to developmental defects of neural crest cells. Therefore, all the patients with OAVS should have thoroughly cardiovascular examinations with special attention to the patients with vertebral anomalies or associated extra-craniofacial anomalies.*

Keywords: *Oculoauriculovertebral spectrum, Cardiovascular malformations, Congenital heart diseases, Goldenhar syndrome, Hemifacial microsomia, Frequency, Type*

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Oculo-Auriculo-Vertebral Spectrum (OAVS) is a complex developmental disorder that affects craniofacial structures derived mainly from the first and second branchial arches and their derivatives[1-3]. It has a wide range of organ anomalies and a varying degree of severity[1-3]. It is characterized by mostly unilateral malformations of the facial structures (including hemifacial microsomia) and sometimes with extra-craniofacial malformations (including spine, heart, kidney, bone, and other anomalies)[2,4]. The most severe form of OAVS is Goldenhar syndrome[1-3]. The etiology is still uncertain, although, thought to be heterogeneous and multifactorial[2,4]. Though most cases are sporadic, genetic history is also found in 1 to 2% of the cases[1-4]. It is approximately 3% of newborns having congenital malformations[5], while the birth prevalence of OAVS has been estimated to be between 1 in 5,642[3] and 1 in 44,907[6] live births.

Cardiovascular malformation is common in patients with OAVS, however, it is only occasionally reported [3,5-25]. Since the occurrence and the type of cardiovascular malformations may cause serious complications[13,25], the objective of this systematic review was to define the evidence of frequency, type, and risk factors of cardiovascular malformations in the OAVS.

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Material and Method

Data sources

A systematic literature search was conducted using electronic databases through the PubMed and the Scopus between 1952 and June 2017 using the medical subject heading of cardiovascular malformations or congenital heart diseases and oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum]. The eligible papers in all languages were included and screened. The titles and abstracts

of the 302 relevant articles were assessed independently by two authors (MP and KW) to identify potentially relevant articles for which full text publications were retrieved. Duplicated papers were removed. Reference lists of included papers were examined for additional relevant papers that may have been missed in the database search.

Definitions

Cardiovascular malformation was defined as a defect in the structure of the heart or great vessel that was present at birth. OAVS was defined as an apparent unilateral malformation of the facial structure (including hemifacial microsomia) which was a mild form. When OAVS malformation has an extra-craniofacial involvement including, spine, heart, kidney, bone, and other anomalies, this type of OAVS was considered to be a severe form.

Study selection

All published prospective and retrospective studies of the frequency and type of cardiovascular malformations or congenital heart diseases in patients with OAVS were considered for inclusion in this review. When a study was eligible for inclusion, two authors (MP and KW) independently verified the frequency and type of cardiovascular malformations or congenital heart diseases to check for accuracy.

The authors excluded studies which were limited only to clinical features and OAVS patterns without a mention of the frequency and type of cardiovascular malformations or congenital heart diseases. Papers of case report were also excluded because these documents were on subjects beyond the objective of this study. When a study was eligible for inclusion, the two authors independently verified the paper. Disagreements were resolved by discussion.

Data extraction

Data on total number of patients with OAVS, number of cases with cardiovascular malformations, study types (prospective or retrospective), inclusion criteria of OAVS and types of cardiovascular malformations were extracted. In case of a patient with many types of cardiovascular lesions, type of cardiovascular malformation was presented according to the major cardiovascular anomaly of each patient.

Quality assessment

Studies were assessed on completeness of data and origins of the data.

Statistical analyses

The frequency and type of cardiovascular malformations in the patients with OAVS were reported in percentage.

Results

The search combination in the databases found 302 relevant articles. After a thorough evaluation of these articles by using the study selection criteria, the authors excluded 289 articles. Thirteen articles, therefore, met the study selection criteria and were included. After critical review of the full texts, one article was excluded due to incomplete data. Of these 12 papers, there were 10 additional studies found after reference checking. These ten additional studies were not initially retrieved by the original search because they were not indexed in the searched databases. Thus, 22 articles were eligible for the inclusion into this systematic review (Fig. 1).

Of the 22 studies included, 348 (21%; range, 1 to 58%) patients with cardiovascular malformations were found out of a total 1,685 (range, 7 to 294) cases of OAVS (Table 1). The patients who had cardiovascular

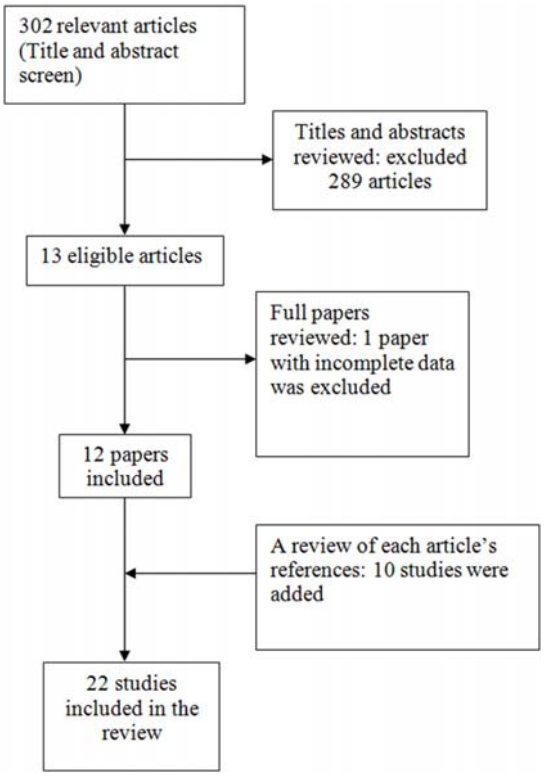

Fig. 1 Flow diagram of the articles included into this systematic review.

Table 1. Frequency and type of cardiovascular malformations in 1,685 patients with Oculo-Auriculo-Vertebral Spectrum (OAVS)

Authors/Years	Study type/ Inclusion criteria of OAVS	Number of patients with OAVS (% of associated extra-craniofacial malformations/ % of vertebral anomalies	Number of cases with cardio vascular malformations (%)	Types of Cardiovascular malformations (numbers)	The patients with CHD having extra-craniofacial malformations (%)
Cohen et al[5]/ 2017	P (hospital based study)/ Expanded spectrum of hemifacial microsomia including mandibular hypoplasia, ear defects, orbital malformations, vertebral, and/or other systemic anomalies	89 (85/47)	26 (29)	VSD (10), ASD (11), coarctation of aorta (3), valvular heart disease (2)	NA
Heike et al[6]/ 2016	R (case-control study)/ Hemifacial microsomia, facial asymmetry, microtia, OAVS, or Goldenhar syndrome	134 (27/NA)	24 (18)	NA	NA
Pegler et al[7]/ 2016	R (hospital based study)/ Two of the following anomalies; orocraniofacial, eye, ear, or vertebral anomalies.	41 (89/66)	15 (37)	VSD (5), ASD (6), TOF (2), PDA (2)	30
Beleza-Meireles et al[8]/2015	R (hospital based study)[a]/ Hemifacial microsomia, ear anomalies, ocular defects, orofacial clefts, and vertebral anomalies.	51 (31/20)	8 (16)	VSD (4), ASD (1), PS (1), coarctation of aorta (1), PDA (1)	67
Silva et al[9]/ 2015	R (hospital based study)/ Two of the following anomalies; orocraniofacial, eye, ear, or vertebral anomalies.	19 (90/35)	7 (37)	NA	71
Barisic et al[10]/ 2014	P (population-based study)/Microtia or ear anomalies, and major anomalies of the OAVS spectrum (hemifacial microsomia, epibulbar dermoids, or vertebral malformations).	259 (70/24)	72 (28)	VSD (31), ASD (13), PS (5), TOF (4), TGA (4), dextrocardia (6), Coarctation of aorta (3), AV septal defects (6)	NA

OAVS = Oculo-Auriculo-Vertebral Spectrum; P = prospective study; R = retrospective study; VSD = ventricular septal defect; ASD = atrial septal defect, secundum type; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; DORV = double outlet right ventricle; PS = pulmonic stenosis; PA = pulmonary valve atresia; AS = aortic valve stenosis; APVR = anomalous pulmonary venous return; LV = left ventricle; PDA = patent ductus arteriosus; AV septal defects = atrioventricular septal (AV canal) defects; CHD = congenital heart disease; LSVC = left superior vena cava

[a] clinical Genetics centers; [b] cardiac department in major medical centers; [c] all patients were severe and PA/hypoplasia of pulmonary arteries were found in four of six cases; [d] two patients died without surgical intervention.

Table 1. Cont.

Authors/Years	Study type/ Inclusion criteria of OAVS	Number of patients with OAVS (% of associated extra-craniofacial malformations/ % of vertebral anomalies	Number of cases with cardio vascular malformations (%)	Types of Cardiovascular malformations (numbers)	The patients with CHD having extra-craniofacial malformations (%)
Rosa et al[11]/ 2011	R (hospital based study)[b]/Two of the following anomalies; orocraniofacial, eye, ear, or vertebral anomalies.	12 (NA/NA)	7 (58)	NA	NA
Rosa et al[12]/ 2010	R (hospital based study)/ Two of the following anomalies; orocraniofacial, eye, ear, or vertebral anomalies.	33 (NA/NA)	13 (39)	VSD (1), ASD (2), TOF (2), TGA (1), PS (1), PA (1), double inlet LV (1), PDA (2), AV septal defect (1), cortriatriatum (1)	NA
Rooryck et al[13]/2010	R (French national recruitment study)/ Microtia or preauricular tag, hemifacial microsomia, or vertebral anomalies.	91 (NA/35)	25 (27)	VSD + ASD (12), TOF + situs inversus+ dextrocardia+ TGA (13)	NA
Digilio et al[14]/ 2008	P (hospital based study)/ Two of the following anomalies ; orocraniofacial, eye, ear, or vertebral anomalies.	87 (NA/45)	28 (32)	VSD (6), ASD (3), TOF (6), TGA (2), PA (1), DORV (2), PAPVR or TAPVR (2), Scimitar syndrome (2), dextrocardia (2), coarctation of aorta (1), PDA (1)	NA
Engiz et al[15]/ 2007	P (hospital based study)/Craniofacial, auricular and vertebral anomalies.	28 (NA/39)	11 (39)	NA	NA

OAVS = Oculo-Auriculo-Vertebral Spectrum; P = prospective study; R = retrospective study; VSD = ventricular septal defect; ASD = atrial septal defect, secundum type; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; DORV = double outlet right ventricle; PS = pulmonic stenosis; PA = pulmonary valve atresia; AS = aortic valve stenosis; APVR = anomalous pulmonary venous return; LV = left ventricle; PDA = patent ductus arteriosus; AV septal defects = atrioventricular septal (AV canal) defects; CHD = congenital heart disease; LSVC = left superior vena cava

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Table 1. Cont.

Authors/Years	Study type/ Inclusion criteria of OAVS	Number of patients with OAVS (% of associated extra-craniofacial malformations/% of vertebral anomalies	Number of cases with cardio vascular malformations (%)	Types of Cardiovascular malformations (numbers)	The patients with CHD having extra-craniofacial malformations (%)
Stromland et al[16]/2007	P (hospital based study)/Two of the following anomalies; orocraniofacial, eye, ear, or vertebral anomalies.	18 (89/67)	6 (33)	VSD (3), TOF (1), coarctation of aorta (1), PDA (1)	83
Touliatou et al[17]/2006	R (hospital based study)/Craniofacial anomalies and microtia.	17 (53/23)	3 (18)	NA	NA
Tasse et al[18]/ 2005	P (hospital based study)/Microtia or preauricular tag, hemifacial microsomia, or vertebral anomalies.	53 (NA/19)	8 (15)	VSD (4), dextrocardia+ ASD + PDA (1), AS (1), coarctation of aorta (1), VSD + PDA (1)	NA
Werler et al[19]/2004	R (multi-centers case-control study)/ Hemifacial microsomia, facial asymmetry, Goldenhar syndrome, or unilateral anotia/microtia.	239 (NA/13)	49 (21)	NA	NA
D'Antonio et al[20]/1998	R (hospital based study)/Facial, maxillary, orbit, oral cavity, ear, neck, palatal functions, and larynx	41 (29/NA)	7 (17)	NA	NA
Araneta et al[21]/1997	R (case-control study)/ Multiple diagnoses of OAVS (ICD-9 codes)	7 (86/57)	3 (43)	VSD (1), ASD (1), dextrocardia (1)	67
Kumar et al[22]/1993	R (hospital based study)/Genetic or autopsy database.	32 (NA/NA	6 (19)	PA (1), TGA (1), DORV (2), asplenia syndrome (1), TAPVR (1)	NA
Morrison et al[23]/1992	R (hospital based study)/Ear anomaly with one other malformation.	25 (NA/NA)	8 (32)	VSD (4), ASD (1), PS (1), TOF (1), Complex CHD with LSVC (1)	NA

OAVS = Oculo-Auriculo-Vertebral Spectrum; P = prospective study; R = retrospective study; VSD = ventricular septal defect; ASD = atrial septal defect, secundum type; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; DORV = double outlet right ventricle; PS = pulmonic stenosis; PA = pulmonary valve atresia; AS = aortic valve stenosis; APVR = anomalous pulmonary venous return; LV = left ventricle; PDA = patent ductus arteriosus; AV septal defects = atrioventricular septal (AV canal) defects; CHD = congenital heart disease; LSVC = left superior vena cava

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Table 1. Cont.

Authors/Years	Study type/ Inclusion criteria of OAVS	Number of patients with OAVS (% of associated extra-craniofacial malformations/% of vertebral anomalies	Number of cases with cardio vascular malformations (%)	Types of Cardiovascular malformations (numbers)	The patients with CHD having extra-craniofacial malformations (%)
Rollnick et al[24]/1987	R (hospital based study)/Hemifacial microsomia, Goldenhar syndrome, or other OAVS	294 (44/19)	14 (5)	NA	NA
Greenwood et al[25]/1974	R (hospital based study)[b]/Oculoauricular dysplasia	13 (NA/NA)	7 (54)	VSD (1), TOF[c] (6)	100[d]
Grabb[3]/1965	R (hospital based review and retrospective survey)/Diagnoses of pediatricians	102 (7/NA)	1 (1)	NA	NA
Total	P, R	1,685	348 (21)		

OAVS = Oculo-Auriculo-Vertebral Spectrum; P = prospective study; R = retrospective study; VSD = ventricular septal defect; ASD = atrial septal defect, secundum type; TOF = tetralogy of Fallot; TGA = transposition of the great arteries; DORV = double outlet right ventricle; PS = pulmonic stenosis; PA = pulmonary valve atresia; AS = aortic valve stenosis; APVR = anomalous pulmonary venous return; LV = left ventricle; PDA = patent ductus arteriosus; AV septal defects = atrioventricular septal (AV canal) defects; CHD = congenital heart disease; LSVC = left superior vena cava
[a] clinical Genetics centers; [b] cardiac department in major medical centers; [c] all patients were severe and PA/hypoplasia of pulmonary arteries were found in four of six cases; [d] two patients died without surgical intervention.

malformations also had a higher frequency of vertebral anomalies[11,15] and associated extra-craniofacial abnormalities in other organ systems[9,10,17]. The conotruncal heart anomalies (cardiac defects in the outflow parts of the heart) of cardiovascular malformations were significantly associated with OAVS in the population-based studies[11,26].

Discussion

This present study revealed that prevalence of cardiovascular malformations among OAVS patients ranged from 1% to 58%[3,5-25]. This variability of the prevalence rates is probably due to the different diagnostic criteria, methodology and sample size of the respective studies (Table 1). Grabb[3] found only one case having congenital heart disease among 102 patients with OAVS in his landmark retrospective data. Rollnick et al[24] included majority of mild cases of isolated microtia and other minor ear anomalies among their OAVS patients which might justify the low frequency of cardiovascular malformations to be only 5%. In contrast, Rosa et al[11] reported a high frequency of cardiovascular malformations (58%) which was probably due to referral bias by using tertiary center with more severe cases as sources of data in their study[11,25].

Although cardiovascular system and other associated anomalies including, spine, kidney, and bone, were the structures that did not derive from the first and second branchial arches or their derivatives[1-3], these extra-craniofacial structures derived from cell populations developing in the same period with craniofacial development. These findings suggest that many different cell populations may be disturbed during fetal development in the pathogenesis of OAVS in association with cardio-vascular malformations and other extra-craniofacial anomalies[1-3].

OAVS in the patients with cardiovascular malformations also had a higher frequency of vertebral anomalies[10,14] and of associated extra-craniofacial abnormalities in other organ systems[8,9,16]. Therefore,

the presence of vertebral anomalies, as well as associated extra-craniofacial anomalies in other organ systems, appears to increase the risk of cardiovascular malformations, which should then be screened for associated cardiovascular malformations[16,21,25].

In the large population based studies[10,26], the conotruncal heart anomalies (cardiac defects in the outflow parts of the heart) were significantly associated with OAVS in parallel with earlier reports[7,10,12,14,22,25]. Some authors believe that the higher frequency of conotruncal heart defects (specifically, Tetralogy of Fallot or truncus arteriosus) among patients with OAVS may be related with an abnormality in neural crest cell migration during craniofacial development in fetal life[4,27-28].

Conclusion

Cardiovascular malformations occur commonly in the patients with OAVS and some patients may be related to developmental defects of neural crest cells. Therefore, all the patients with OAVS should undergo thorough cardiovascular examinations with special attention to the patients with vertebral anomalies or associated extra-craniofacial anomalies.

What is already known on this topic?

The frequency of cardiovascular malformations in patients with OAVS was in the range of 5% to 58%.

What this study adds?

The frequency of cardiovascular malformations in the patients with OAVS ranges from 1% to 58%. Conotruncal heart defects were commonly associated with OAVS than in general population.

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Potential conflicts of interest

None.

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รูปวิปริตของหัวใจและหลอดเลือดในผู้ป่วย Oculo-Auriculo-Vertebral Spectrum: ทบทวนอย่างเป็นระบบ

มนัส ปะนะมณฑา, อรรฆิศา ไชกิจภิญโญ, ยุทธพงศ์ วงศ์สวัสดิวัฒน์, จันดาวอน สุกกะเสิม, อวยพร ปะนะมณฑา, กุณฑล วิชาจารย์

ภูมิหลัง: *รายงานความชุกและชนิดของรูปวิปริตของหัวใจและหลอดเลือดในผู้ป่วย Oculo-Auriculo-Vertebral Spectrum (OAVS) ยังมีความแตกต่างกันมากและยังไม่มีการศึกษาทบทวนอย่างเป็นระบบในรายงานเหล่านั้น*

วัตถุประสงค์: *เพื่อศึกษาทบทวนอย่างเป็นระบบในรายงานความชุกและชนิดของรูปวิปริตของหัวใจ และหลอดเลือดในผู้ป่วย OAVS*

วัสดุและวิธีการ: *ค้นหาอย่างเป็นระบบในฐานข้อมูล PubMed and Scopus ช่วงระหว่าง พศ. 2495 ถึง มิถุนายน พ.ศ. 2560 โดยใช้คำค้นว่า Cardiovascular malformations or congenital heart diseases and oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum]*

ผลการศึกษา: *พบรายงานวิจัยที่เกี่ยวข้องจำนวน 22 รายงาน แต่ละรายงานมีจำนวนผู้ป่วยตั้งแต่ 7-294 ราย รวมผู้ป่วย OAVS ทั้งหมด 1,685 รายและมีผู้ป่วยที่มีรูปวิปริตของหัวใจและหลอดเลือดร่วมด้วยจำนวน 348 (21%, range 1%-58%) ราย ผู้ป่วยที่มีรูปวิปริตหัวใจและหลอดเลือดมักมีความผิดปกติของกระดูกสันหลัง หรือความผิดปกติ ของอวัยวะอื่นๆ นอกเหนือจากความพิการของใบหน้าและศีรษะ ในรายงานใหญ่ที่ศึกษาในประชากรพบว่า ชนิดของรูปวิปริตหัวใจและหลอดเลือดที่พบในผู้ป่วย OAVS บ่อยกว่าประชากรทั่วไปอย่างมีนัยยะสำคัญทางสถิติคือ conotruncal heart diseases ซึ่งเป็นความผิดปกติของทางออกของหัวใจ เช่น tetralogy of Fallot หรือ truncus arteriosus เป็นต้น*

สรุป: *รูปวิปริตของหัวใจและหลอดเลือดพบได้บ่อยในผู้ป่วย OAVS และในผู้ป่วยบางรายอาจมีต้นเหตุมาจากความผิดปกติของกลุ่มเซลล์ neural crest ระหว่างเป็นตัวอ่อนในครรภ์ ดังนั้นควรตรวจหาภาวะรูปวิปริตของหัวใจและหลอดเลือดในผู้ป่วย OAVS ให้ละเอียด และเน้นเป็นพิเศษในผู้ป่วยที่มีความผิดปกติของกระดูกสันหลัง หรือในผู้ป่วยที่มีความผิดปกติของอวัยวะอื่นๆ นอกเหนือจากความพิการของใบหน้าและศีรษะ*