Oculo-Auriculo-Vertebral Spectrum in Patients with Congenital Heart Defects

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Abstract

Background: **There have been few studies evaluating the frequency of oculo-auriculo-vertebral spectrum (OAVS) in patients with congenital heart defects (CHDs).**

Objective: **To verify the frequency of OAVS in a sample of patients with major heart malformations.**

Methods: **We evaluated a prospective cohort of patients with CHD admitted in a pediatric cardiac intensive care unit (ICU) in Brazil. The diagnosis of OAVS was made based on the clinical data, considering standard criteria. The patients that met these criteria were submitted to high resolution GTG-Banding karyotype and fluorescence in situ hybridization for 22q11.2 microdeletion. Fisher's exact test ($P < 0.05$) was used for the statistical analysis.**

Results: **During the period of evaluation, 330 patients were hospitalized for the first time in the ICU, but thirty of them did not participate in the study. Of the 300 patients that constituted the final sample, OAVS was verified in 3 cases (1%). All presented normal cytogenetic studies.**

Conclusion: **OAVS seems to be a frequent condition among patients with CHDs. However, we cannot exclude the possibility that the frequency of OAVS found in our study might have been underestimated due to the low rate of prenatal detection of CHDs and the limited access of patients to appropriate health care in our region. Future prospective studies with well defined clinical criteria and subjects with mild and major defects will be important to assess the role of OAVS in the general population of subjects with heart malformations. (Arq Bras Cardiol 2010; 95(4): 436-440)**

Key words: **Heart defects, congenital; Goldenhar, syndrome; infant, newborn, diseases.**

Introduction

Congenital heart defects (CHDs) are the most frequent congenital anomalies at birth and represent an important public health problem. Its general incidence ranges from 4 to 14 per 1,000 live births. Severe and moderate forms of CHDs that will require advanced and, commonly, immediate care account for approximately 3 to 4 per 1,000 live births[1,2]. They represent an important cause of admission in pediatric intensive care units (ICUs)[3]. Nevertheless, the etiology of CHDs remains in general poorly understood[4,5]. An association with known causes, such as chromosomal abnormalities, gene and multifactorial conditions, maternal diseases and teratogens is made in only 10 to 25% of the cases [6,7].

Oculo-auriculo-vertebral spectrum (OAVS) [OMIM #164210][8] is a heterogeneous condition clinically characterized by a non-random association of abnormalities that especially involves the face, eyes, ears and spine[9-12]. Also known as Goldenhar syndrome and hemifacial microsomia, it is considered a relatively common defect of blastogenesis[13]. Its estimated birth prevalence has been shown to range from 1/5,600 to 1/26,550 newborns[14,15]. CHDs are a frequent feature of OAVS. Their prevalence among these patients has ranged from 5 to 58%[11,12,16-22] and this variability seems to be especially related to the different inclusion criteria used by the researchers[20] and the pathogenetic heterogeneity of the syndrome[12].

Methods

We evaluated the frequency of OAVS in a prospective cohort of patients with CHD admitted in the pediatric cardiac ICU of the *Hospital da Criança Santo Antônio (HCSA)/ Complexo Hospitalar Santa Casa de Porto Alegre (CHSCPA)*, RS, Brazil. The diagnosis of OAVS was made based on the clinical data (physical examination and results of complementary exams such as spine radiography), considering the criteria adopted both by Strömland et al[11] (i.e. features in ≥ 2 of the oro-cranio-facial, ocular, auricular, and vertebral areas) and by Digilio et al[12] (i.e. presence of at least two of the

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following findings: unilateral microtia, unilateral mandibular hypoplasia, uni- or bilateral epibulbar dermoid, or vertebral malformations). The patients that met these criteria were submitted to a cytogenetic analysis through high resolution GTG-Banding karyotype (≥ 550 bands) and fluorescence *in situ* hybridization (FISH) for 22q11.2 microdeletion, using the DiGeorge/VCFS Region Probe (TUPLE 1) (Vysis, Abbott Molecular Inc.). The cardiac diagnosis was attained based on the results of the echocardiography and in most cases, confirmed through surgical description and/or cardiac catheterization. Fisher's exact test ($P < 0.05$) was used for the statistical analysis. This study was approved by the Ethical Committee of the Hospital.

Results

During a period of 1 year and 4 months, 330 patients were hospitalized for the first time in the pediatric cardiac ICU of the Hospital. Thirty of them did not participate in the study due to the presence of severe heart defect that led to death; to have been discharged from the hospital before the application of the consent, or because the parents chose not to consent. Of the 300 patients that constituted the final sample, OAVS was verified in 3 cases (1%). Their clinical features can be seen in Table 1 and Figure 1. None had a 22q11.2 microdeletion or any other detectable chromosomal abnormality.

Discussion

In the literature, there have been three reports of OAVS frequency in patients with CHDs. Pradat[23] evaluated a sample of 397 Swedish infants with a major cardiac defect and at least one non-cardiac malformation. Patients known to have a chromosomal abnormality were not included in his study and the author found OAVS in two patients (0.5%). Meberg et al[24] studied a sample of 360 Norwegian patients with a CHD diagnosed among 35,218 infants born alive during a 15-year period. All were clinically investigated according to a standard protocol and the suspected cases of CHD underwent a more comprehensive investigation and were referred for echocardiography. OAVS was described in one patient (0.3%). Güçer et al[25] evaluated autopsies of Turkish patients born alive and diagnosed with a CHD during a period of 26 years. Of the 305 cases reviewed, OAVS was identified in only one patient (0.3%).

These investigated cohorts were very heterogeneous and different from the one evaluated by us. The adopted selection criteria were variable and incorporated, in some cases, the exclusion of subjects with chromosomal abnormalities or only the inclusion of patients with associated extracardiac anomalies[23]. The studied populations were also different. Meberg et al[4], for example, evaluated patients diagnosed with CHD in a consecutive sample of live births, while Güçer et al[5] focused only on subjects with a CHD who were autopsied. Differently from our study, the majority of others were retrospective and none presented the description of the criteria adopted for OAVS diagnosis. In spite of all these aspects, when we compared the OAVS frequency in our study (1%) with the others (ranging from 0.3 to 0.5%), we did not find a statistical difference between them.

Table 1 - Clinical findings observed in the patients with oculo-auriculo-vertebral spectrum (OAVS) of our study

Clinical features	Patients *		
	1	2	3
Sex	M	M	M
Age	11m	2m	2m
OAVS criteria			
- Strömland et al (2007)[5]	3/4	2/4	4/4
- Digilio et al (2008)[4]	3/4	2/4	3/4
Hypotonia	+		+
Growth retardation	+	+	+
Unilateral mandibular hypoplasia	+	+	+
Facial palsy		+	+
Upslanting palpebral fissures	+		
Telecanthus	+	+	
Choanal atresia	+		
Cleft lip and palate		+	
High arched palate	+		
Hypoplastic tongue			+
Microretrognathia		+	
Upper eyelid coloboma			+
Epibulbar dermoid			+
Preauricular pits			+
Preauricular skin tags		+	+
Ear canal agenesis		+	
Unilateral microtia	+	+	
Dysplastic ears			+
Esophageal atresia		+	
Tracheoesophageal fistula		+	
Laryngotracheomalacia		+	
Radial abnormalities			+
Cervical-vertebral abnormalities	+		+
Rib alterations		+	+
Accessory spleen	+		
Congenital heart defect	+	+	+
PA + VSD	+		
Cor triatriatum		+	
DILV			+

** They correspond to the patients from the Figure 1; M: male; m: months; PA + VSD: pulmonary atresia associated to ventricular septal defect; DILV: double inlet of left ventricle.*

CHDs described in OAVS frequently belong to the group of conotruncal and septal defects. Tetralogy of Fallot and ventricular septal defects are considered the main abnormalities. Complex abnormalities, such as cardiac laterality defects in the setting of heterotaxy are also common[12,16,17,20,26-28]. In our series, two of the three patients

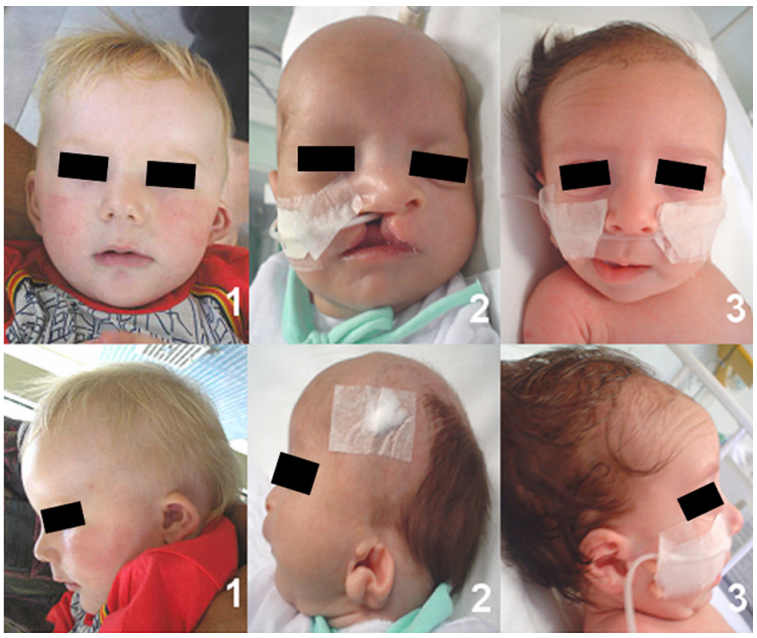

Figure 1 - Front and lateral view of the patients with oculo-auriculo-vertebral spectrum (OAVS): patient 1 at 11 months of age (pulmonary atresia associated to ventricular septal defect), patient 2 at 2 months of age (cor triatriatum) and patient 3 at 2 months of age (double inlet of left ventricle). Note especially the unilateral mandibular hypoplasia (1 to 3), microtia (1 and 2), preauricular skin tags (2 and 3), cleft lip (2) and small upper eyelid coloboma (in the right eye of the patient 3).

presented a conotruncal heart defect, which consisted of a ventricular septal defect associated to pulmonary atresia (patient 1) and a double inlet of left ventricle (patient 3). This last one represents, to our knowledge, the first description of a patient with both OAVS and this heart defect. Similarly, there have been no previous reports of subjects with OAVS and cor triatriatum, the additional cardiac abnormality observed in our sample (patient 2). This patient presented the "classic" form of cor triatriatum, i.e., an accessory chamber joined the left atrium directly and received the pulmonary veins which egress through the opening in the "membrane". Interestingly, the embryonic error that leads to cor triatriatum is thought to be similar to that observed in anomalous pulmonary venous return[29], a type of heart abnormality significantly associated to OAVS[12]. Some authors believe that the higher frequency of conotruncal heart defects among patients with OAVS may be related with an abnormality in neural crest cell migration, which would explain the presence of other craniofacial findings observed in the syndrome, such as face, eye and ear abnormalities[9,30].

All OAVS patients in our sample died before the end of the second year of life, two of them (patient 1 and 3) due to complications directly related to their CHDs. It is known that these defects represent the main cause of death of OAVS patients, which usually happens early into the first years of life[13,17,19] as also verified in our series. Their death could be related to the severity of the CHDs, as conotruncal defects, for example, are frequent in OAVS and are associated with a high mortality[2].

Conclusions

OAVS seems to be a frequent condition among patients with CHDs. In our study, its frequency was similar, for example, to that of 22q11.2 deletion syndrome (OMIM #188400/ #192430)[8] (around 2%), a genetic disease also highly associated to conotruncal heart defects[31]. However, we cannot exclude the possibility that the frequency of OAVS found in our study might have been influenced by the low rate of prenatal detection of CHDs and the limited access of patients with these defects to appropriate health care in our region[31]. These factors, associated to the severity of many heart defects found in patients with OAVS, could have lead to an underestimation of the frequency of this disease.

Our study only evaluated patients with major cardiac malformations and necessity of hospitalization at an ICU. Future prospective studies with well-defined evaluation criteria and subjects with mild and major defects will be important to assess the role of OAVS in the general group of patients with heart malformations.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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