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Prevalence of Congenital Heart Disease and Pulmonary Hypertension in Down's Syndrome: An Echocardiographic Study

Nilda Espinola-Zavaleta, MD, PhD[1,2], María Elena Soto, MD, PhD[1,2], Angel Romero-Gonzalez, MD[2], Lidia del Carmen Gómez-Puente, MD[3], Luis Muñoz-Castellanos, MD[2], Aasha S. Gopal, MD[4], Candace Keirns, MD[5], and Eulo Lupi-Herrera, MD[1]

[1]ABC Medical Center I.A.P, Cardiovascular Division, Mexico City, Mexico
[2]National Institute of Cardiology "Ignacio Chavez", Echocardiography in Out-Patient Clinic, Immunology Department, Embryology Department, Mexico City, Mexico
[3]The John Langdon Down Foundation, A.C, Pediatric Department, Mexico City, Mexico
[4]St. Francis Hospital, Cardiac Imaging, New York, USA
[5]Massachusetts General Hospital, Interpreters Service, Boston, USA

Background: Down's syndrome (DS) is a genetic anomaly, which undergoes increased morbidity and mortality when associated with congenital heart disease (CHD). The aims of the study were to determine the prevalence of CHD and pulmonary hypertension (PH) in DS.

Methods: One hundred twenty-seven patients with DS living in Mexico City were evaluated by physical exam, electrocardiogram and echocardiogram.

Results: CHD was found in 40%. In 80% (n = 102) PH was present [systolic pulmonary artery pressure (SPAP) of 47 ± 19 mm Hg and mean pulmonary artery pressure (MPAP) of 32 ± 11 mm Hg]. Patients with CHD and PH were classified as having 1) no shunt (n = 18) with SPAP of 37 ± 9 mm Hg and MPAP of 25 ± 6 mm Hg and 2) with shunt (n = 26) with PASP of 57 ± 29 mm Hg and MPAP of 38 ± 19 mm Hg ($p \leq 0.001$). In those without CHD or with CHD without shunt (n = 76), SPAP was 37 ± 19 mm Hg and the MPAP 25 ± 6 mm Hg. The prevalence of PH in DS was 5.9% at one year and 15% at 10 years. The odds ratio of PH in DS with CHD was 7.3 vs. 3 without CHD.

Conclusion: DS has a high prevalence of CHD and PH. PH prevalence increases when it is associated with CHD. The pathophysiology of PH in DS without CHD should be studied in the near future. Echocardiography is an indispensible tool for evaluation of DS.

KEY WORDS: Down's syndrome · Echocardiogram · Pulmonary hypertension · Congenital heart disease · Shunt.

Introduction

Down's syndrome (DS) was first described in 1866 by John Langdon Down. It is the most common chromosomal abnormality.[1] The incidence of DS in world literature varies from 1/600 to 800;[2] in Mexico it is reported to be 1/420 to 480.[3] Because of a defect in the distribution of chromosomes in DS affected individuals have three copies of chromosome 21, clinical manifestations are variable and cannot establish the type of chromosomal abnormality, therefore the diagnosis requires a karyotype determination.[4]

The prevalence of congenital heart disease (CHD) in DS is approximately 43%.[5] The most common cardiac malformations associated with DS include atrioventricular canal, patent ductus arteriosus and atrial septal defect (ASD) and ventricular septal defect (VSD).[6] Some of the congenital heart conditions have intra and extra-cardiac shunts that can lead to pulmo-

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• Address for Correspondence: María Elena Soto, ABC Medical Center I.A.P, Cardiovascular Division, Investigation Department, Sur 136 No. 116, Colonia Las Américas, Delegación Alvaro Obregón, México City 01120, Mexico Tel: +52-55-732911, Fax: +52-55-730994, E-mail: mesoto50@hotmail.com

nary hypertension (PH) due to volume overload of pulmonary circulation and to structural remodeling of pulmonary vasculature.[1)7)8)] However, PH has also been found in patients with DS without associated CHD.[9)] The best non-invasive method to detect CHD and to determine the systolic pulmonary artery pressure (SPAP) at present is echocardiography. Early diagnosis of congenital heart conditions and PH can be crucial for effective treatment that provides optimum quality of life in DS patients.

The objectives of our study were to determine the prevalence of CHD and PH by clinical, electrocardiographic and echocardiographic evaluation in the DS at a moderate altitude of Mexico City.

Methods

All parents and/or guardians of DS subjects signed informed consent for inclusion in the study.

Patients

Between January of 2010 and January of 2013, 127 patients who had no echocardiographic study and accepted to participate were selected, including 64 males (50.4%) and 63 females (49.6%). All had undergone genetic study, were born and lived in Mexico City (altitude: 2240 meters).

Clinical histories were taken on all patients including data of file such as the gyneco-obstetric history of the mother, history of hypothyroidism, mass surface index and complete physical exam.

Prospectively an otorhinolaryngeal examination of the upper airway was performed on all patients aged more than five years (95/127). The criteria used to define upper airway obstruction were: narrowing of nasopharynx and tonsillar, adenoidal and nasal conchae enlargement.

A twelve lead surface standard electrocardiogram and a transthoracic echocardiogram were performed.

Transthoracic echocardiogram

Transthoracic echocardiogram was performed in the supine position, without sedation or supplemental oxygen and with a responsible family member present. The equipment used was a Philips iE33 ultrasound system (Philips Medical Systems, Bothell, WA, USA) with an S5-1 chest wall transducer. Each study included M-mode, two dimensional, pulsed, color and continuous wave Doppler elements. Left ventricular ejection fraction (LVEF) was assessed from an apical 4-chamber image using a Simpson's method (LVEF ≥ 50% was considered normal). Diastolic function was evaluated with pulsed Doppler on an apical 4-chamber image with the sample volume placed at the tips of the mitral leaflets. E and A wave velocities (rapid mitral filling and atrial contribution to mitral flow, respectively), E wave deceleration time and isovolumetric relaxation time were measured. Normal patterns included an E/A ratio of 1.0 to 1.49, deceleration time > 160 msec and isovolumentric relaxation time ≥ 220 msec. Type I diastolic dysfunction was identified when the E/A ratio was ≤ 0.99. Type II was associated with a pseudo-normal E/A ratio (1.0–1.49) with a deceleration time < 160 msec and an E/A ratio of ≥ 1.5 defined type III diastolic dysfunction.[10)] The right ventricular diastolic diameter was measured from an apical 4-chamber image at a level above the tricuspid valve. A normal value was considered to be ≤ 40 mm. Right ventricular systolic function was evaluated on the basis of tricuspid annular peak systolic excursion (TAPSE) measured from M-mode tracing taken from an apical 4 chamber view with ≥ 16 mm as normal. The peak velocity of the tricuspid ring was measured using the S wave velocity from the apical 4-chamber image captured by tissue Doppler (normal value was considered to be ≥ 10.5 cm/sec).[11)] Tricuspid regurgitation peak velocity was used to determine SPAP. This was done calculating the systolic transtricuspid gradient using the modified Bernoulli equation, and then adding an assumed or calculated right atrial pressure.[12)13)] The final value of the SPAP was the average of three consecutive determinations. In cases with VSD or patent ductus arteriosus the SPAP was estimated as the systemic systolic arterial pressure minus the gradient of the shunt.[14)] Systolic PH was classified as 1) mild: 30–40 mm Hg, 2) moderate: 50–69 mm Hg, and 3) severe ≥ 70 mm Hg.[15)] This classification of PH was based a consensus of experts from the American College of Cardiology Foundation/American Heart Association 2009 meeting.[15)16)] The mean pressure of the pulmonary artery (MPAP) was calculated with the following formula: 0.61 × SPAP + 2 mm Hg and was considered normal when it was ≤ 25 mm Hg.[17)]

The diagnosis of congenital heart defects was established in the following sequence: situs, atrioventricular and ventriculoarterial concordance, associated defects (ASD and VSD and patent ductus arteriosus) and valve lesions (stenosis and/or regurgitation).[18)] The Qp/Qs was calculated using a previously described formula.[19)] All studies were performed by cardiologist-echocardiographers.

Statistical analysis

Numeric variables were evaluated with a Gaussian distribution with measurements of central tendency considering mean and 1-standard deviation and in categorical variables with percentages. Bivariate analysis was adjusted according to the distribution. Student's t or the Mann-Whitney U tests were used with categorical variables as well as χ^2 with Yates' correction or the Fisher exact test. The 95% confidence interval (CI 95%) was calculated for the difference of proportions and the statistical power of a bilateral test to compare two proportions in a transverse study, prevalence of PH and CHD, prevalence ratios with CI 95%, and odds ratio with CI 95% for PH and for each of the variables found to be significant.

Results

Mean ages of the patients, mothers and fathers and the

number of maternal pregnancies are described in Table 1. DS was the result of trisomy 21 in 97% of the subjects and translocation in 3%. Five patients (4%) reported faintness, 3 (2.4%) chest pain and 2 (1.6%) occasional palpitations. In 82% the cardiovascular examination was normal. In the remaining subjects, acrocyanosis and clubbed fingers were found. Of the subjects more than 5 years of age, 86% (82/95) had obstruction of the upper airway caused by tonsillar enlargement (70%, 67/95) or enlargement of tonsils and nasal conchae (16%, 15/95).

According to the clinical evaluation, 81.1% (103/127), were in the New York Heart Association functional class I, 17.3% were in class II and 1.6% in class III (Table 1).

Table 1. Demographic findings (n = 127)

Age (years ± SD)	
Patients	16.4 ± 12
Mothers	32.1 ± 6.8
Fathers	35.7 ± 8.0
Number of maternal pregnancies (median, interval)	2 (1–9)
Weight (kg)	44.4 ± 20.0
Height (m)	1.3 ± 0.2
Body surface index (m^2)	23.0 ± 7.1
NYHA class	
I	103.0 (81.1%)
II	22.0 (17.3%)
III	2.0 (1.6%)
Without medications	114.0 (89%)
With medications	13.0 (11.2%)
ENT evaluation (95/127)	
Tonsillar enlargement	67.0 (70%)
Enlargement of tonsils and nasal conchae	15.0 (16%)
Patent upper airway	13.0 (14%)

SD: standard deviation, NYHA: New York Heart Association, ENT: ear nose and throat, kg: kilograms, m: meters, m^2: square meters

Table 2. Electrocardiographic findings (n = 127)

	n (%)
Normal	58 (46)
RBBB	43 (34)
RBBB and DRV	10 (8)
DRV	13 (10)
DRV and DLV	3 (2)

RBBB: right bundle branch block, DRV: dilated right ventricle, DLV: dilated left ventricle

Therapy

89.8% (114/127) received no medical treatment (Table 1). Angiotensin converting enzyme inhibitors, loop diuretics or spironolactone were prescribed in 11.2% (13/127). None received permanent oxygen (≥ 18 hours). Eight (6.3%) were hypothyroid and were treated with levothyroxine.

The electrocardiogram was normal in 46% (58/127). Right bundle branch block and enlarged right heart were present in the majority of the remaining patients (Table 2).

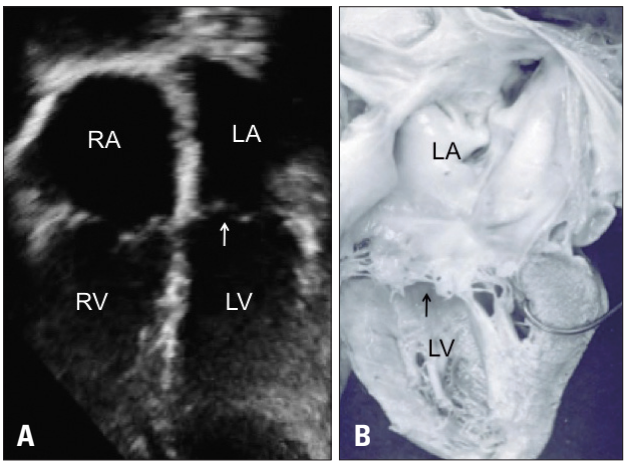

Fig. 1. Anatomo-echocardiographic correlation of an isolated cleft of the septal leaflet of the mitral valve. A: Echocardiographic image showing the cleft of the septal mitral leaflet with a white arrow. B: Internal view of anatomic specimen showing left cardiac cavities, the black arrow points the cleft of the septal mitral leaflet. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.

Table 3. Echocardiographic findings (n = 127)

Variable	Without congenital heart defect n (%) = 76 (60)	With congenital heart defect n (%) = 51 (40)	*p*
Aortic diameter (mm)	26.0 ± 7.7	34.4 ± 9.6	0.001
Left atrial diameter (mm)	28.0 ± 5.0	34.0 ± 8.0	NS
Left ventricular ejection fraction (%)	67.0 ± 6.0	65.0 ± 6.0	NS
E/A ratio	1.6 ± 0.5	1.6 ± 0.5	NS
LVDD (mm)	33.8 ± 12.0	36.0 ± 7.0	NS
TAPSE (mm)	20.0 ± 4.0	19.0 ± 4.0	NS
S wave velocity (cm/sec)	7.5 ± 2.9	7.5 ± 3.6	NS
SPAP (mm Hg)	37.2 ± 12.0	50.5 ± 15.0	0.001
MPAP (mm Hg)	26.0 ± 6.0	34.4 ± 16.0	0.001

Values are expressed as mean ± standard deviation. LVDD: left ventricular diastolic diameter, TAPSE: tricuspid annular peak systolic excursion, SPAP: systolic pulmonary artery pressure, MPAP: mean pulmonary artery pressure, S: systolic, NS: not significant

ECHOCARDIOGRAPHIC FINDINGS (Table 3)

LVEF and TAPSE were normal in all subjects. The S wave velocity was abnormal (7.5 ± 3.2 cm/sec) in 84% (107/127). Left ventricular diastolic function was abnormal in 68% (86/127). Twelve (9.5%) had type I dysfunction, 17 (13.5%) type II and 57 (45%) type III.

Associated CHD was found in 40% (51/127). Patent ductus arteriosus, ASD and isolated cleft of the anterior mitral leaflet (Fig. 1) were the most frequent. The VSD was perimembranous in all, and in 3 the VSD reached the left ventricular inlet (Table 4). The Qp/Qs was 2.0 ± 0.7.

The SPAP and the MPAP for the group were 42.5 ± 17 mm Hg and 29 ± 11 mm Hg, respectively. Subjects without associated CHD (76/127) had a SPAP and a MPAP of 36.5 ± 8.9 mm Hg and 25.3 ± 5.6 mm Hg, respectively. In those cases with CHD the SPAP was 48 ± 20 mm Hg and the MPAP 33 ± 12 mm Hg ($p \leq 0.001$).

One hundred two subjects (80%) had PH with a SPAP of 47 ± 19 mm Hg and MPAP of 32 ± 11 mm Hg. When no CHD (58/102) the SPAP was 40 ± 7 mm Hg and the MPAP was 28 ± 4.6 mm Hg. In patients with CHD (44/102) the PASP and MPAP were 51 ± 19 mm Hg and 35 ± 12 mm Hg, respectively ($p \leq 0.001$). For patients with DS, CHD, and PH (44/102), we classified them into two groups: 1) those without shunts (18/44), in whom the SPAP was 37 ± 9 mm Hg and the MPAP 25 ± 6 mm Hg, and 2) those with shunts (26/44), in whom the SPAP and the MPAP were 57 ± 29 mm Hg and 38 ± 19 mm Hg, respectively ($p \leq 0.001$) (Fig. 2). In the miscellaneous group, which included seventy-six patients that did not have CHD (n = 58) or had heart defects without shunts (n = 18) the SPAP was 37 ± 19 mm Hg and the MPAP 25 ± 6 mm Hg, respectively.

The prevalence of PH in DS was 5.9% at one year and 15% at 10 years. The odds ratio (OR) of PH in DS with CHD was 7.3 vs. 3 without CHD. In subjects with DS and CHD, the probability of developing PH was 46%, while in those with-

Table 4. Associated congenital heart defects (n = 51)

Type of heart defect	n	%
Without shunt		
Isolated cleft of the anterior mitral leaflet	8	16
Prolapse of the anterior mitral leaflet	6	12
Bicuspid aortic valve with raphe	1	2
Patent foramen ovale	3	6
With shunt		
Ventricular septal defect	7	14
Rastelli type A atrioventricular septal defect	6	12
Ostium secundum type atrial septal defect		
Isolated	5	10
Associated with other defects	4	8
Patent ductus arteriosus		
Isolated	2	4
Associated with other defects	9	18

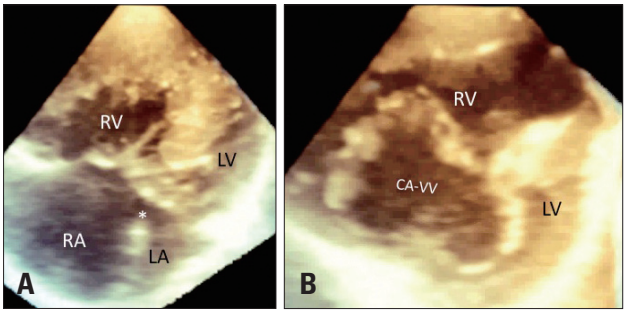

Fig. 3. Three-dimensional transthoracic images of a mixed type of Rastelli A and B unbalanced atrioventricular septal defect (A) with a common atrioventricular valve of five leaflets (B). The asterisk shows the ostium primum. RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, CA-VV: common atrioventricular valve.

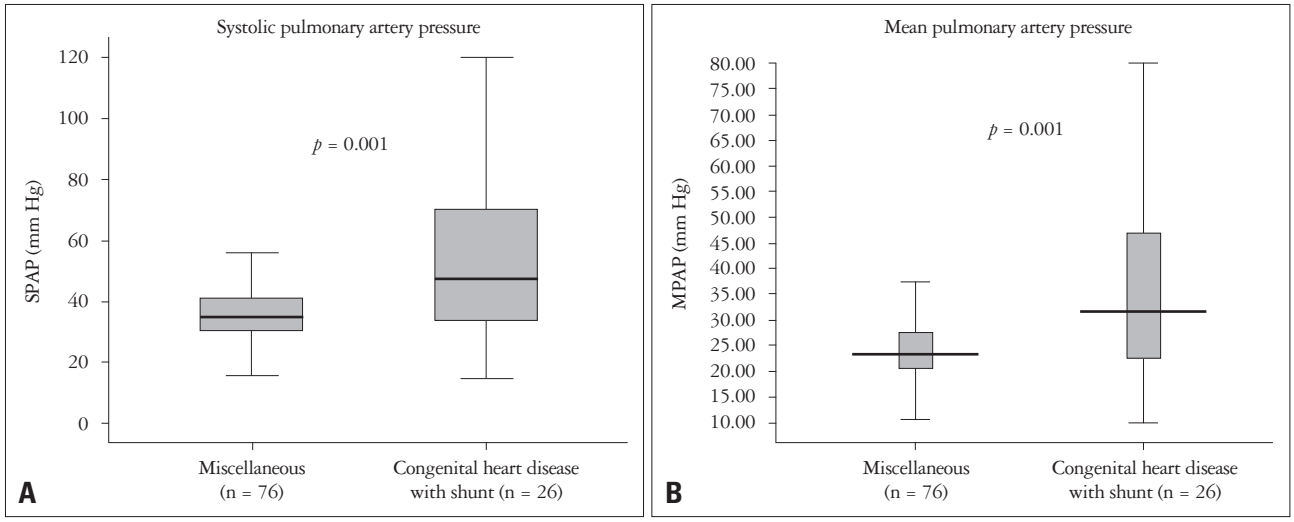

Fig. 2. Graphical representation of the systolic (A) and mean (B) pulmonary artery pressure between the group of patients with shunt and the miscellaneous group. There is a statistically significant difference between groups, $p = 0.001$.

out CHD it was 53%. The OR of PH prevalence in DS and CHD was 1.88 (CI 95% 1.02–2.1, $p \leq 0.001$) and the OR of PH prevalence in DS without CHD was 0.50 (CI 95% 0.46–0.70, $p \leq 0.02$) and the OR of PH prevalence in generally in DS was 1.96 (CI 95% 1.1–1.98, $p \leq 0.0001$).

After three years of follow-up one patient had died as a result of PH and right heart failure.

Discussion

While DS can be associated with a number of other pathological entities, CHD is the principal cause of increased morbidity and mortality. From 19 to 43% of patients with DS have some type of congenital heart defect.[6] In our study we found that 40% of the subjects had associated CHD, which is consistent with the values reported in the literature.[4)20)] In contrast to other reports from Latin America in which ASD was the heart defect most commonly found (24%),[4] in our study patent ductus arteriosus was the abnormality of highest prevalence (22%), probably related with the moderate altitude of Mexico City,[21] with ASD in second place (18%), VSD (14%) in third and atrioventricular septal defect (12%) in fourth place (Fig. 3). In Europe and countries of Anglo-Saxon origin atrioventricular septal defect is the congenital malformation of the heart most commonly associated with DS and varies from 40–80%.[6] In our series 10% of the subjects had multiple heart defects, a much lower percentage than the reported by Frid et al.[6] (30%).

Patients with DS have a much higher risk of developing PH than in the general population.[21] In our series 80% had PH, and it was of greater degree in those with CHD and shunt when compared with patients with DS without CHD, and patients with CHD and without shunts. In the literature it is reported that 90% of patients with DS and CHD develop PH.[22] In this study the prevalence of PH was 5.9% per year with the probability of its development 2.4 times greater in patients with DS and CHD than in those without CHD. Weijerman et al.[5] and Cua et al.[23] found that the prevalence of PH in neonates with DS was 1.2 to 5.2%, while the prevalence in the general population is 0.1%.

In our series, the systolic function of the two ventricles assessed by LVEF and systolic displacement of the tricuspid ring was normal in all DS patients. However, the fact that S wave velocity was decreased may suggest perhaps subclinical right ventricular contractile dysfunction.[11)24)] The left ventricular diastolic dysfunction found in 68% of our patients, needs further investigation.

In 1958, Heath and Edwards[25] described the pathological changes of pulmonary vasculature found in patients with intra and extra-cardiac shunts PH. At the altitude of Mexico City (2240 meters) De Micheli et al.[26] reported histological alterations of the media of the pulmonary arteries with moderate PH and of both the media and intima with severe PH. It is noteworthy that patients with DS develop PH even in the absence of congenital heart defects, as we found in 46% of the patients. However, when DS patients were grouped with those with CHD without shunts, the prevalence of PH was higher (76/127 = 59%). In this group some authors have demonstrated pulmonary hypoplasia to be the main cause of PH.[20)22)27)] Obstruction of the upper airway is commonly associated with DS and may contribute to obstructive sleep apnea and chronic hypoxemia, eventually leading to pulmonary vascular disease.[9)27)] In our series 86% of the patients had upper airway obstruction, a similar figure rate to what is reported in the literature.[9)28)29)] It is noteworthy that our patients were evaluated at moderately high altitude where the lower partial pressure of inhaled oxygen could lead to a higher incidence of PH. However, this was not corroborated for DS nor previously in obese or in chronic obstructive pulmonary disease patients.[3)4)30)31)]

Clinical and electrocardiographic signs of PH were uncommon and consequently these diagnostic modalities rarely corroborated it. Our study demonstrated that the echocardiogram is an indispensible tool in the detection of CHD, diagnosis of PH and its hemodynamic repercussions on the right heart.

Conclusion

DS has a high prevalence of CHD and PH when compared to the general population. The risk of PH increases 2.4 time when congenital heart defects are present, but it does not seem to be affected by moderate altitude. The etiopathogenesis of PH in patients with DS without CHD remains to be clarified. Its mechanisms will be the focus of investigation in the near future. Echocardiography should be considered to be an indispensible non-invasive tool for the integral evaluation of DS.

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