Heart Malformations in Children With Down Syndrome

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Introduction and objectives. A longitudinal, retrospective, observational descriptive study was done at the National Institute of Pediatrics in Mexico City to determine the incidence, type of heart disease and clinical course in patients with Down syndrome (DS), and to compare the findings with data from other countries. Down syndrome is a disease caused by trisomy of chromosome 21. The frequency of presentation in one in 650 live births. Frequency in the general population is about 1%. Cardiac malformation is the main cause of mortality in the first 2 years of life.

Patients and method. In a 5-year period 275 patients (aged neonate to 13 years) were diagnosed with DS. Diagnosis was based on echocardiogram, catheterization, genetics, surgical exploration or necropsy. Age, sex, clinical manifestations, mother's age, type of heart defect were recorded.

Results. Of the 275 children with DS, 160 had congenital heart disease. The most frequent cardiopathies were interauricular septal defect (IASD), interventricular septal defect (IVSD) and patent ductus arteriousus (PDA) (90%). In contrast to the data from other countries, only 14 patients (8%) had atrioventricular septal defect (AVSD). Twenty-five patients died (15%) from sepsis and cardiogenic shock.

Conclusions. At our institute 58% of the children with DS had congenital heart malformation. The most frequent cardiopathies were different from those reported in other countries.

Key words: *Down syndrome. Congenital cardiopathy. Cardiac malformation.*

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Malformaciones cardíacas en los niños con síndrome de Down

Introducción y objetivos. Se realizó un estudio retrospectivo, longitudinal, observacional y descriptivo en el Instituto Nacional de Pediatría de la ciudad de México donde se da a conocer la incidencia, el tipo de cardiopatía y la evolución clínica en los pacientes con síndrome de Down (SD) y se compara con otras comunicaciones de la bibliografía.

El SD es una enfermedad que presenta trisomía en el cromosoma 21. La frecuencia de presentación es de uno de cada 650 nacidos vivos. El riesgo de recurrencia es del 1% en la población general. La malformación cardíaca es la mayor causa de mortalidad en los primeros 2 años de la vida.

Pacientes y método. En un lapso de 5 años se diagnosticaron 275 niños con SD. Las variables estudiadas fueron: edad, sexo, manifestaciones clínicas, edad materna, tipo de cardiopatía, diagnósticos por ecocardiograma, cateterismo cardíaco, estudio cromosómico, quirúrgico o autopsia.

Resultados. De los 275 niños, cursaron con cardiopatía 160 (58%). Las cardiopatías que se presentaron con mayor frecuencia fueron la comunicación interauricular (CIA), comunicación interventricular (CIV) y persistencia del ductus arterioso (PDA) (90%); únicamente 14 casos (9%) correspondieron a defectos de la tabicación auriculoventricular, a diferencia de lo observado en otros países. La manifestación clínica más frecuente fue la insuficiencia cardíaca. El 15% de los pacientes (n = 25) fallecieron, y las causas más frecuentes fueron el choque séptico y cardiogénico.

Conclusiones. El 58% de los niños con SD de nuestro instituto cursaron con cardiopatía congénita. La presentación de las cardiopatías más frecuentes difiere de la de otros países.

Palabras clave: *Síndrome de Down. Cardiopatía congénita. Malformaciones cardíacas.*

INTRODUCTION

First described in 1866, Down syndrome is a condition characterized by trisomy of chromosome 21.[1,2] Among all cases, 95% are primary trisomy and 5%

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ABBREVIATIONS

ASD: atrial septal defect.
VSD: ventricular septal defect.
PDA: patent ductus arteriosus.
AVSD: atrioventricular septal defect.

are translocation and mosaic forms (3% and 2%, respectively).[3] The overall incidence of Down syndrome is one case in every 650 live births, although this rate varies according to the mother´s age. In mothers 45 years of age or older, the incidence reaches one in every 30 live births.[2,3] The risk of recurrence is 1% in the general population.[4]

The clinical manifestations of Down syndrome are numerous and can present in any body system. The most significant include intellectual impairment, short stature, heart disease, digestive disorders and orthopedic abnormalities. Heart disease is, without a doubt, the main factor contributing to a favorable or unfavorable course in these patients. Among all cases of congenital heart disease, 4%-10% are associated with Down syndrome, and 40%-60% of Down syndrome patients present congenital heart disease. Cardiac malformation is the principal cause of mortality in the first two years of life.[5,6] In Mexico, the most frequent cardiac abnormalities in Down syndrome patients are patent ductus arteriosus (PDA), ventricular septal defect (VSD), and atrial septal defect (ASD). This contrasts with the situation in Anglo-Saxon and European countries, where the predominant cardiac malformation (40%-70%) is atrioventricular septal defect (AVSD), with partial atrioventricular canal defect (ostium primum ASD with mitral cleft) being the most frequent among these.[5-10]

It is important to be familiar with the incidence and anatomic characteristics of congenital heart disease in Down syndrome, as well as the associated complications and causes of morbidity and mortality, in order to apply preventive measures and to improve the patients quality of life. Thus, we describe the experience of our center. Other factors can also influence survival in these patients, such as the socioeconomic situation, female sex and low birth weight.[11] The main causes of death are heart failure, sepsis, and pulmonary hypertension. This last process appears earlier in patients with AVSD and results in a reduction in survival of up to 58%.[12-14] The most common non-cardiac features associated with Down syndrome are digestive tract malformations.

The aim of this article is to determine the incidence, type and clinical course of congenital heart disease affecting Down syndrome patients in our geographical area and to compare these data with those reported in the literature.

PATIENTS AND METHOD

A descriptive, observational, longitudinal, retrospective study was performed between January 1994 and December 1998.[15] Medical records from 275 children with Down syndrome assisted at the Instituto Nacional de Pediatría (National Institute of Pediatrics) in Mexico D.F. were reviewed. Among these patients, 160 presented structural heart disease. Diagnoses were based on echocardiography, cardiac catheterization, chromosome study, surgery and autopsy results. Patients who did not have a complete clinical, genetic or cardiologic study, and those over 16 years old were excluded. Data on age, sex, place of birth, age of the mother and number of gestations, type and frequency of heart disease, clinical characteristics, associated abnormalities, type of treatment and clinical course were analyzed.

For the statistical analysis, the proportions and respective 95% confidence intervals (CI) were obtained for each of the pathologies studied. The χ^2 test of homogeneity was used to determine the homogeneity of the proportions.[16]

To compare the hypothesis of equality of proportions of AVSD, VSD, tetralogy of Fallot, PDA and ASD reported in a study from the Children's Hospital Boston and a study covering the Atlanta area, a two-way test for comparing two proportions from independent populations with the Z_C statistic was used to compare the data found in the present study. In order to maintain the error rate per experiment at α_E=0.05, we used the Bonferroni adjustment, in which α_E was divided by two, the number of comparisons (Mexico vs Boston and Mexico vs Atlanta), such that the error per comparison was $\alpha_C=\alpha_E/2=0.025$.[16,17]

RESULTS

Among the 275 children with Down syndrome seen at our hospital, 160 (58%) presented some type of congenital heart disease. The cardiologic diagnosis was made at a mean of one year of age (range, 0-13 years), with 74% of the patients under one year of age (SD, 2.0). The male-to-female ratio was 1:1. The patients came from 13 states in the Republic of Mexico.

Children with Down syndrome were born mainly to young mothers (34%), 16 to 25 years of age. A total of 48 patients (30%) were first-born children. Among the 160 patients studied, 72 (45%) were diagnosed on the basis of clinical criteria. Genetic study demonstrated regular trisomy 21 in 70 cases (43%), translocation trisomy 21 in ten (6%) (including five 14/21, three 21/21, and two 12/21), and mosaic trisomy 21 in

eight (5%).

Among the 160 patients, 74% had isolated cardiac abnormalities and 26% had associated cardiac abnormalities. The most frequent isolated heart defect was ASD in 39 cases (24%), with a predominance of the ostium secundum type (14 cases). Isolated VSD was present in 35 cases (22%). The perimembranous form was the most frequent VSD in the series (six isolated and five associated).

Patent ductus arteriosus was the defect most commonly associated with other cardiopathies (34 cases). Atrioventricular septal defect was the fourth in frequency, with a total of 14 cases, corresponding to 8.7%. Three other cardiac abnormalities were observed: bilateral pulmonary lesion, tetralogy of Fallot, and aortic stenosis. The most frequently associated heart abnormalities were ASD with PDA in 10% (17 cases), followed by VSD with PDA, AVSD with PDA, VSD with ASD and four other different cases. Among these cardiac abnormalities, the two first associations, ASD+PDA and VSD+PDA were more frequent than AVSD+PDA, VSD+ASD, or others. Overall, PDA was present in 67 cases, ASD in 64, VSD in 51, AVSD in 14 and other cardiac abnormalities in 7 cases (Table 1).

The most common clinical finding was heart failure in 53 patients (33%). A total of 58 patients (36%) were asymptomatic. Other findings include respiratory difficulty in 24 (15%), cyanosis-hypoxia in 16 (10%), heart murmur in 7 (4%), retarded growth in one and neonatal cholestatic syndrome with AVSD in one. Pulmonary hypertension was observed in 50% of patients (80 cases). The abnormalities most frequently associated with pulmonary hypertension were AVSD at an early age, seen in 8 patients (89%), VSD plus PDA in 8 (80%), PDA in 22 (67%), and AVSD plus PDA in 3 (60%). Less frequently seen were ASD plus aberrant left subclavian artery, PDA plus aberrant left subclavian artery and bilateral pulmonary lesion (43%), ASD in 16 children (41%), VSD in 14 (40%), VSD plus ASD in 2 (40%) and PDA plus ASD in 4 (24%).

Echocardiography provided diagnostic information in 121 cases (75%) (Figures 1 and 2). The most frequent associated extracardiac malformations were umbilical hernia in seven patients, followed by anorectal malformation. In 131 (91%) patients, the initial

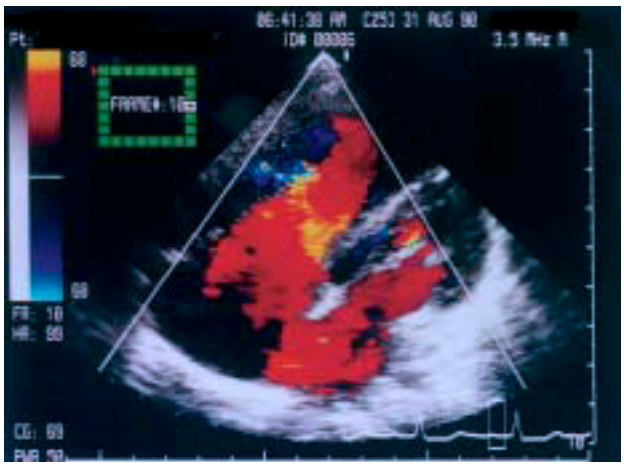

Fig. 1. Four-chamber view showing a large secundum type defect in the atrial septum. Blood flow crossing the atrial septal defect is apparent on Doppler echocardiography.

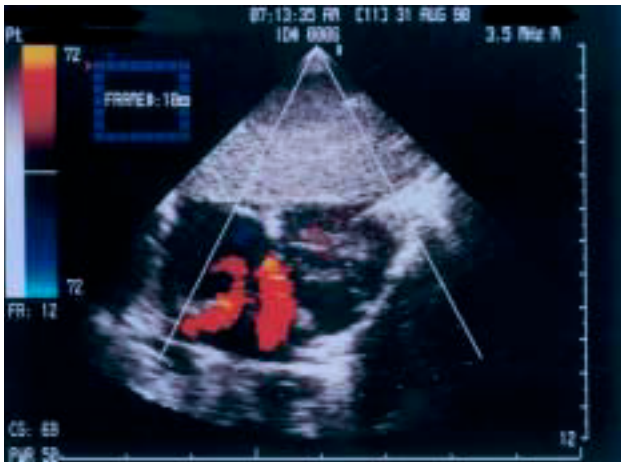

Fig. 2. Subcostal four-chamber view with Doppler echocardiography demonstrates blood flow crossing two defects, a primum atrial septal defect and a ventricular septal defect of the inflow tract in a patient with an atrioventricular septal defect.

TABLE 1. **Incidence of congenital heart diseases in Down syndrome**

Cardiopathy	Sample	Proportion	95% CI	
			Lower limit	Upper limit
Isolated	119	0.74	0.68	0.81
ASD	39	0.24	0.18	0.31
VSD	35	0.22	0.15	0.28
PDA	33	0.21	0.14	0.27
AVSD	9	0.06	0.02	0.09
Others[a]	3	0.02	0.00	0.04
Associated	41	0.26	0.19	0.32
ASD+PDA	17	0.11	0.06	0.15
VSD+PDA	10	0.06	0.02	0.10
AVSD+PDA	5	0.03	0.00	0.06
VSD+ASD	5	0.03	0.00	0.06
Others[b]	4	0.03	0.00	0.05
Total	160			

[a]Includes BPL (n=1), TF (n=1), and AoS (n=1).
[b]Includes ASD+PS (n=1), ASD+ALS (n=1), PDA+ASD+VSD (n=1).
ASD indicates atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; BPL, bilateral pulmonary lesion; AoS, aortic stenosis; PS, pulmonary stenosis; PDA, patent ductus arteriosus; ALS, aberrant left subclavian; TF, tetralogy of Fallot.

TABLE 2. **Comparison among Down syndrome congenital heart diseases**

	México (n=160)[a]				Boston (n=666)[b]				Atlanta (n=226)[c]				Roma[d]
			95% CI				95% CI%				IC del 95%		
Cardiopathy	Frequency	Proportion	Lower limit	Upper limit	Frequency	Proportion	Lower limit	Upper limit	Frequency	Proportion	Lower limit	Upper limit	Proportion
ASD	61	0.38	0.31	0.46	16	0.02	0.01	0.04	18	0.08	0.04	0.11	0.03-0.10
VSD	48	0.30	0.23	0.37	171	0.26	0.22	0.29	79	0.35	0.29	0.41	0.20-0.30
PDA	34	0.21	0.15	0.28	19	0.03	0.02	0.04	16	0.07	0.04	0.10	0.03-0.10
AVSD	14	0.09	0.04	0.13	328	0.49	0.45	0.53	102	0.45	0.39	0.52	0.50-060
Complete		12				262							
Partial		2				51							
Others							15						
TF	1	0.01	–0.01	0.02	68	0.10	0.08	0.13	9	0.04	0.01	0.07	0.05-0.10
DCRV							6	0.01	0.00	0.02			
AoCo						5	0.01	0.00	0.01				
Others	2	0.01	0.00	0.03	53	0.08	0.06	0.10	2	0.01	0.00	0.02	

[a]Instituto Nacional de Pediatría (Mexico D.F., Mexico), five-year study. [b]Children;s Hospital Boston (USA), fifteen-year study. [c]Atlanta area (USA). [d]Hospital Bambino Gesú (Rome, Italy).
ASD indicates atrial septal defect; VSD, ventricular septal defect; AoCo, aortic coarctation; AVSD, atrioventricular septal defect; DCRV, double-chambered right ventricle; PDA, patent ductus arteriosus; TF, tetralogy of Fallot.

therapy was medical treatment and in 25 patients (9%) surgery was performed. Closure of the patent ductus arteriosus was carried out in ten patients.

Twenty-five patients died (15%). The main causes of death were septic or cardiogenic shock (12 and 10 patients, respectively). Autopsies performed in two patients confirmed the clinical diagnosis of VSD with PDA in a patient who died of bronchial pneumonia and complete AVSD with no other associated anomalies in a patient who died of septic shock.

DISCUSSION

The incidence of Down syndrome congenital heart disease in our center is high (58%), though it is within the range described in the world literature (40%-60%). This high incidence is attributed to the fact that the study was performed in a referral center for Mexico.

Down syndrome is associated with maternal ages at the extremes of the childbearing period. In our analysis it was most frequent in young mothers, since a high number of young, primiparous women are accepted by our center for genetic study and counseling. The majority of our patients were diagnosed with congenital heart disease during the first year of life (74%), even though this is not a maternity hospital. Not all the children with Down syndrome were diagnosed by cytogenetic study (72 cases). Diagnosis is based on clinical criteria in our center and cytogenetic analysis is performed only on children born to young mothers, first-born children, and children with a family member having the same pathology.

Atrial septal defect, VSD and PDA accounted for 90% of the cardiac abnormalities observed in Down syndrome. The most frequent was PDA, combining both isolated and associated cases. Atrial septal defect was the most common isolated cardiac defect (33% of the total) and ostium secundum ASD was the most frequent type. Ventricular septal defect was present in 29% of patients, with the perimembranous form predominating. Atrioventricular septal defect accounted for only 9% of Down syndrome congenital heart disease in our series, an incidence that contrasts with reported data from hospitals in Spain, England, Holland and the USA (Table 1). The embryology and anatomy of VSD, ASD and PDA are quite different from that of AVSD.[8,18,19] Our high incidence of PDA is not seen in other countries. In European and North American hospitals, it is the fourth most frequent congenital heart disease.[14,20-22] Table 2 compares the incidence of Down syndrome cardiac abnormalities in this study and in some parts of the USA and Europe (Italy).

With regard to ASD, values reported in the present study in Mexico vary considerably from those in studies from Boston, Atlanta, and Rome. Whereas in Mexico 38% of patients presented this cardiac defect, the figures for Boston, Atlanta, and Rome are 2%, 8% and 3%-10%, respectively. The values for VSD from Mexico, Boston, Atlanta, and Rome are similar, however, at 20%-35%. Data for PDA show a similar pattern in Boston, Atlanta and Rome, with reported values of 3%-10%, whereas in Mexico the percentage was up to six fold higher. AVSD values in Boston and Atlanta were found to be comparable, at 45% and 49%, whereas in Rome the incidence was somewhat higher (50%-60%). We highlight that in our study the AVSD value was 9%, much lower than in these other

TABLE 3. **Comparison between proportions of Down syndrome congenital heart diseases in Mexico and other areas**

Cardiopathy	Mexico (n=160)[b]	Boston (n=666)	*P*<.0125	Atlanta (n=226)	P<.0125
ASD	0.38	0.02	[a]	0.08	[a]
VSD	0.30	0.26		0.35	
PDA	0.21	0.03	[a]	0.07	[a]
AVSD	0.09	0.49	[a]	0.45	[a]
TF	0.01	0.10	[a]	0.04	[a]

[a]Highly significant differences, *P*<.0125.
[b]Instituto Nacional de Pediatría, Mexico D.F.
ASD indicates atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus; TF, tetralogy of Fallot.

areas. It is noteworthy that studies performed in Boston and Rome found the same proportion of heart abnormalities. In Boston, Atlanta, and Rome, the most frequent malformations were AVSD and VSD, whereas in the Instituto Nacional de Pediatría, the most frequent were ASD and VSD. Tetralogy of Fallot is uncommon in Mexico and Atlanta, in contrast to Boston, where the incidence is higher (Table 2).

Table 3 confirms the results in Table 2: the situation in Mexico differs from that of Boston and Atlanta for all types of heart abnormalities (*P*<.125) with the exception of VSD, which showed no significant differences as compared to these referral hospitals in the USA.

The teratogenic determinant that interferes with adequate formation of the endocardial cushions (the malformation of AVSD) in Down syndrome does not exist in Mexico or other Latin American countries. There is still no clear explanation for this fact. Genetic factors, specific embryological mechanisms and cell characteristics can determine the type of cardiac malformation.[7] Nevertheless, ethnic and geographic factors may also influence the formation of these abnormalities, as would be the case of the high altitude of Mexico D.F., where the low oxygen levels predispose to a higher incidence of PDA.[5] Among the 67 patients with congenital heart disease involving PDA, 54 came from the State of Mexico and Mexico D.F., geographical areas that are over 2400 meters above the sea level.

Mortality is higher in patients with congenital heart disease and associated extracardiac anomalies (chromosome syndromes). However, when the associated heart abnormalities are left-to-right shunts (as in most of our cases), the prognosis is more favorable than when there is associated AVSD, which is linked with pulmonary hypertension, a condition in itself related to high mortality.[23] That is why the prognosis for Down syndrome patients with heart defects in terms of mortality is better in our area than in other countries.

Congenital heart defects reduce survival in Down syndrome patients by 72%. ASD and VSD in the early phases are associated with better survival rates than AVSD. AVSD implies a poor prognosis in 58%, because complete correction is required before the age of six months to avoid residual lesions (most frequently mitral regurgitation) and because of the high incidence of associated pulmonary hypertension (89%).[14,24] Children with Down syndrome heart disease often have increased pulmonary vascular resistance and develop considerable pulmonary vascular injury at early ages; thus, AVSD has a good prognosis in patients who receive early surgical treatment.[25]

The clinical course of Down syndrome heart disease in our center and the outcome of medical or surgical treatment are more favorable when the condition is detected early and pulmonary hypertension, a frequent complication (50% of our cases), is avoided.[26-28]

The most frequent extracardiac malformations observed in the present study were related to the digestive tract, a finding consistent with results reported in the literature.[2,3] Immediate surgical treatment is not as frequent in our patients as in other countries[11] because of our high incidence of VSD and ASD, which require medical treatment initially. Our short-term survival is 85%.

It is important for the people entrusted with the care and management of Down syndrome patients with heart disease to be aware of the factors related to a poor clinical course. This will enable early diagnosis and the initiation of medical or surgical treatment as soon as possible. This is the main objective to strive in order to provide children with Down syndrome the high quality of life they deserve.[29]

CONCLUSIONS

The incidence of congenital heart disease in patients with Down syndrome was high in our center (58%), though within the range published in the literature (40%-60%). Patent ductus arteriousus, ASD, and VSD accounted for 90% of Down syndrome heart abnormalities in our setting, a rate that differs from previous reports.[6,10,12,18,19,22,26] The isolated defect seen most often was ASD (24%), and the most frequent isolated and associated abnormality was PDA (42%). Atrioventricular septal defect was found in 9% of our patients, a value that contrasts with the incidence of this defect in other countries. Pulmonary hypertension was a frequent complication (50%) that occurred most often in patients with AVSD (89%). The main causes of death were septic and cardiogenic shock. Early diagnosis and treatment of congenital heart disease is of prime importance to improve the quality of life of children with Down syndrome.

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