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 arteriosus (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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**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%
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. 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 $\chi^2$ test of homogeneity was used to determine the homogeneity of the proportions.

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 $\alpha_E=0.05$, we used the Bonferroni adjustment, in which $\alpha_E$ divided by two, the number of comparisons (Mexico vs Boston and Mexico vs Atlanta), such that the error per comparison was $\alpha_C=\alpha_E/2=0.025$.

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 each case.
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
therapy was medical treatment and in 25 patients (9%) surgery was performed. Closure of the patent duc
tus 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 ano-
malies 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 anal-
ysis it was most frequent in young mothers, since a
high number of young, primiparous women are ac-
cepted 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 diag-
nosed by cytogenetic study (72 cases). Diagnosis is
based on clinical criteria in our center and cyto-
genetic analysis is performed only on children born to young
mothers, first-born children, and children with a fa-
mily 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 pre-
dominating. Atrioventricular septal defect accounted
for only 9% of Down syndrome congenital heart dis-
ease in our series, an incidence that contrasts with re-
ported 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 he-
art 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 stu-
dies 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, ho-
wever, 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 2

<table>
<thead>
<tr>
<th>Cardiopathy</th>
<th>Mexico (n=160)*</th>
<th>Boston (n=666)*</th>
<th>Atlanta (n=226)*</th>
<th>Roma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>61 0.38 0.31 0.46</td>
<td>16 0.02 0.01 0.04</td>
<td>18 0.08 0.04 0.11</td>
<td>0.03-0.10</td>
</tr>
<tr>
<td>VSD</td>
<td>48 0.30 0.23 0.37</td>
<td>171 0.26 0.22 0.29</td>
<td>79 0.35 0.29 0.41</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td>PDA</td>
<td>34 0.21 0.15 0.28</td>
<td>19 0.03 0.02 0.04</td>
<td>16 0.07 0.04 0.10</td>
<td>0.03-0.10</td>
</tr>
<tr>
<td>AVSD</td>
<td>14 0.09 0.04 0.13</td>
<td>328 0.49 0.45 0.53</td>
<td>102 0.45 0.39 0.52</td>
<td>0.50-0.60</td>
</tr>
<tr>
<td>Complete</td>
<td>12 262</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Others</td>
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<tr>
<td>TF</td>
<td>1 0.01 -0.01 0.02</td>
<td>68 0.10 0.08 0.13</td>
<td>9 0.04 0.01 0.07</td>
<td>0.05-0.10</td>
</tr>
<tr>
<td>DCRV</td>
<td></td>
<td>6</td>
<td>0.01 0.00 0.02</td>
<td></td>
</tr>
<tr>
<td>AoCo</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 0.01 0.00 0.03</td>
<td>53 0.08 0.06 0.10</td>
<td>2 0.01 0.00 0.02</td>
<td></td>
</tr>
</tbody>
</table>

*Instituto Nacional de Pediatría (Mexico D.F., Mexico), five-year study. †Children’s Hospital Boston (USA), fifteen-year study. ‡Atlanta area (USA). §Hospital Bambino Gesù (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.
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 (\(P < 0.125\)) 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.

### 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 arteriosus, ASD, and VSD accounted for 90% of Down syndrome heart abnormalities in our setting, a rate that differs from previous reports.\(^5,10,12,18,19,22,26\) 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.
REFERENCES