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ORIGINAL ARTICLE

Prevalence of Congenital Heart Diseases in children and adolescentes with Down Syndrome followed up in a pediatric cardiology reference service

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Abstract

Introduction: Down Syndrome (DS) is a genetic syndrome with a high prevalence worldwide and associated with numerous comorbidities, which require greater attention and medical care. Among them, Congenital Heart Defects (CHD) stand out in the population with DS, both for their high prevalence (40-65%) and for their influence on the quality and life expectancy of this population. **Methodology:** This is a retrospective cross-sectional observational clinical study which aim to identify the prevalence of different CHD in the DS population attended at a pediatric cardiology outpatient clinic and to analyze possible factors related to prognosis. There were no exclusion criteria, considering that only patients diagnosed with DS with CHD were included. **Results:** We analyzed 154 patients, 75 males and 79 females, with statistical differences regarding age, weight and length at admission being smaller in females. Weight at the time of surgery was associated with mortality, being lower in patients who died. Total atrioventricular septal defect (AVSD) was the most prevalent CHD and the only congenital heart disease that was statistically associated with mortality. **Conclusion:** The most frequent CHD was AVSD, according to the main literature data. Total AVSD and surgical weight were associated with mortality.

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INTRODUCTION

The incidence of Down Syndrome (DS) is estimated to be 1 in every 700 live births and shows a significant increase when related to advanced maternal age, reaching up to 1 in every 30 children of mothers over 45 years of age.[1] Thus, due to the constant increase in the average maternal gestational age,[2] there has been an increase in its incidence, which makes it necessary to advance studies and knowledge about the trisomy 21 and its complications.

Patients with DS have a higher incidence of pathological conditions such as thyroid disease, heart disease, Alzheimer's disease, hypertension, leukemia, metabolic disorders and gastrointestinal disorders.[3,4] The clinical presentation is heterogeneous, varying in number and severity.[5] Such systemic organic dysfunctions and malformations can affect patients with Down syndrome in isolation or it may coexist in the most diverse combinations, and the signs and/or symptoms of the diseases can be confused with characteristics inherent to the genetic condition, such as hypotonia, for example. Therefore, it is important to perform an early diagnosis of the syndrome so that these pathologies can be quickly screened, identified and properly managed by specialists. Among these conditions, congenital heart disease (CHD) is the most prevalent and remains one of the greatest challenges to be faced in the health care of DS patients, with a prevalence of 40-65%[6,7] and, in itself, it is capable of directly influencing both the prognosis and survival of patients, since it is the greatest cause of morbidity and mortality in the first two years of life[1,8]. In addition, some factors secondary to CHD, such as greater susceptibility to pulmonary infections, further aggravate the clinical condition and prognosis of DS patients when compared to individuals without this condition[9]. There is a consensus in the literature that advanced maternal age, drug use during pregnancy and consanguinity are risk factors for the emergence of congenital heart disease[1]. Given the high prevalence of CHD in children with DS, it is essential to perform a cardiological evaluation as soon as the syndrome is identified. In the neonatal period, the main findings that raise clinical suspicion of this type of alteration include heart murmur, cyanosis, tachypnea and arrhythmia.[10,11] However, these signs are not always present in the first few days, which can delay the diagnosis of heart disease and, consequently, increase the risk of developing complications such as heart failure, pneumonia, cardiac arrhythmias and pulmonary arterial hypertension.[1,12] Confirmation of the diagnosis and distinction between the types of CHD present can be performed by means of echocardiography, or even, when the syndrome is identified during prenatal care, by fetal echocardiography.

To enable continuous improvement in the treatment of children with CHD associated with DS, it is important to evaluate and correlate data regarding the type of heart disease, interventions performed and clinical evolution of the patients. Thus, the present study aims to contribute to the knowledge of the association between congenital heart disease and DS in our environment, as well as the evolution and follow-up of this population.

METHODOLOGY

A retrospective, cross-sectional, observational clinical study was conducted, with data collected from the medical records of children and adolescents with DS who were followed up at a Pediatric Cardiology outpatient clinic from January 1, 1996 to December 31, 2020.

The selection of heart disease patients with DS was performed by consulting the Pediatric Cardiology discipline database. After selecting the patients, the medical records were consulted and the following data were collected:

1) ID number of the service;
2) Sex;
3) Date of birth;
4) Age at initial consultation;
5) Nutritional status at the time of initial consultation;
6) Type of congenital heart disease;
7) Age at the time of surgery(ies);
8) Weight at the time of surgery(ies);
9) Evolution: current follow-up; discharge after clinical treatment; discharge after surgical treatment; loss to follow-up; death;
10) Comorbidities;
11) Maternal age at birth.

The age of the patients was stratified according to the SBP criteria as follows: newborns (NB) - age up to 28 days of life; Infants - age between 29 days and 24 full months; Preschoolers - age between 25 months and 59 months and 29 days; Schoolchildren - age between 60 months and 119 months and 29 days; Adolescents - age equal to or greater than 120 months.

We included all children and adolescents with CHD diagnosed by echocardiography and DS, without other associated syndromes, who were registered in the database of the Pediatric Cardiology discipline treated at the service's outpatient clinic during the period described above. Therefore, we have no exclusion criteria. The assessment of the nutritional status of the patients was performed using the Ped(z)® software by Daniel Gräfe[13], based on the criteria of Zemel, B. S. et al[14] and classified according to the standard of the Ministry of Health (2011)[15]. The collected data were entered into an electronic spreadsheet and submitted to statistical evaluation, considering a significance level of 5%.

We used the SAS software version 9.4 to perform the statistical analyses. We chose to use the mean and standard deviation for variables with normal distribution and use of parametric tests, and the median, first and third quartiles for variables that did not present normal distribution and use of nonparametric tests. We used the Chi-square or Fisher's exact

test when necessary to verify the association of death with comorbidities and CHD. The same analysis was performed for sex. $p < 0.05$ was considered the significance level.

To perform the univariate and multivariate logistic regression analysis, the same software was used. For multivariate analyses, we considered $p < 0.20$ for CHD and included the most prevalent comorbidities.

RESULTS

A total of 154 patients were analyzed, 75 of whom were males (48.7%) and 79 females (51.3%). We found statistically significant differences in the median age at the first consultation between males aged 4.5 months and females aged 2.2 months. This data was corroborated by weight and length, which also maintained the difference between males with a median weight of 4.95 kilos and length of 59 centimeters and females with 3.67 kilos and 54 centimeters.

The nutritional classification was based on the technical standard from the Ministry of Health (MS, 2011) and we identified that patients older than 28 days admitted to the tertiary service were eutrophic, followed by 11% with thinness and 9% at risk of overweight. On the other hand, among patients younger than 28 days of life, only 42% had adequate weight, 32% with low weight and 24% with very low weight. AVSD was the most prevalent CHD found, accounting for 32.17% of cases (total AVSD 18.99% and partial AVSD 13.18%), followed by PDA with 16.28% and ostium secundum atrial septal defect (OSAC)[15].12%.

In the distribution of CHD between sexes, we observed that there was no significant difference, and total AVSD predominated in both sexes. However, the association between CHD and death demonstrated that total AVSD has a direct relationship with higher mortality and no other CHD presented this association.

No other associated comorbidities were found in 52% of patients with DS and CHD; however, GIT alterations accounted for 16.23%, followed by thyroid diseases with 14.94% and neurological alterations with 10.39%. No comorbidity demonstrated a statistical relationship with the outcome of death in the sample evaluated.

The data show that 46.75% of patients were lost to follow-up or were referred to other services, approximately 12% were discharged from the service after surgical and/or clinical treatment, approximately 20% died from cardiac causes, including immediate postoperative, infections or other causes, and 21.43% continue to be monitored in an outpatient setting. Of the deaths, the percentage among females was 26.58%, almost double that of males, at 13.33%, but without statistical significance in the present study.

The univariate logistic regression model was used after performing the Chi square test to assess the frequencies and associations of CHD and comorbidities with death, and the results are shown in Table 3.

Table 1. Age, weight and length/height between the sexes.

	Age (months)			Weight (Kg)			Length/ Stature (cm)		
Sex	Median	P25	P75	Median	P25	P75	Median	P25	P75
Males	4.5*	1.9	15.2	5.35**	4.95	9.01	59.0 #	50.9	76.0
Females	2.2	1.3	6.8	3.49	2.98	3.67	54.0	49.0	60.3
Total	3.9	1.4	10.1	4.18	3.2	7.06	55.0	50.0	72.0

* p = 0.014 (Mann-Whittney - Male x Female)
** p = 0.005 (Mann-Whittney - Male x Female)
# p = 0.019 (Mann-Whittney - Male x Female)

Table 2. Association between congenital heart disease (CHD) and death.

Variables	Survivors N (%)	Deaths N (%)	*p* value
ASD OS	34 (27.64)	5 (16.1)	0.1877
DSAVT	32 (26.02)	17 (54.8)	**0.0021**
Partial AVSD	31 (25.2)	4 (12.9)	>0.05
IVC	26 (21.14)	10 (32.7)	0.1911
T4F	3 (2.46)	1 (3.2)	1.0
PDA	32(26.02)	10(32.26)	0.4856
Valvular diseases	22(17.89)	6(19.35)	0.8497
Other	24(19.51)	2(6.45)	0.1083

CHD: Congenital heart disease; ASD OS: Ostium Secundum atrial septal defect; AVSD: Total/partial atrioventricular septal defect; VSD: Ventricular septal defect; T4F: Tetralogy of Fallot; PDA: Patent ductus arteriosus.

Table 3. Univariate logistic regression model between the outcome of death and associated factors.

Variables	Estimates	OR	CI	*p*
TAVSD	0.6196	3.453	(1.530 - 7.794)	**0.0028**
Thyroid diseases	-0.2973	0.552	(1.53 - 1.991)	0.3638
GIT disorders	-0.00482	0.99	(0.34 - 2.888)	0.9859
Neurological alterations	-0.7136	0.24	(0.03 - 1.891)	0.1754
OS IASD	-0.3432	0.503	(0.179 - 1.418)	0.1939
VSD	0.2873	1.777	(0.745 - 4.234)	0.1947
PAVSD	-0.3205	0.527	(0.17 - 1.636)	0.2677

Total atrioventricular septal defect: TAVSD; ostium secundum interatrial septum defect: OS IASD; ventricular septal defect: VSD; partial atrioventricular septal defect: PAVSD OS; gastrointestinal tract: GIT.

Table 4. Multivariate logistic regression model between the outcome of death and the associated factors.

Variables	Estimate	OR	CI	*p*
TAVSD	0.5913	3.263	(1.434 - 7.426)	0.0048
Thyroid diseases	-0.2298	0.632	(0.168 - 2.379)	0.497
GIT disorders	0.0202	1.041	(0.337 - 3.218)	0.9441
Neurological alterations	-0.6138	0.293	(0.036 - 2.390)	0.2516

Total atrioventricular septal defect: TAVSD; gastrointestinal tract: GIT.

In Table 4, we used the multivariate logistic regression model between the 3 most prevalent comorbidities with TAVSD, where no associations were found between them.

DISCUSSION

International studies show atrioventricular septal defect (AVSD), ventricular septal defect (VSD) and atrial septal defect (ASD) as the most common CHDs in patients with DS, and despite the similarities seen in the present study with AVSD being the most prevalent CHD, we found PDA as the second most frequent CHD followed by ASD. VSD, the second most prevalent in the literature, ranked fourth among the most frequent CHD in our study population[3].

The best prognosis and longest life expectancy of these children are related both to the type of CHD and to early diagnosis and effective surgical correction. Lower mortality and complication rates have been identified in cases of VSD and PDA[2], while AVSD has a high mortality rate when associated with DS[16]. It is also known that when heart diseases are corrected early, patients have a longer survival rate, while the later the surgical indication is given, the worse the prognosis will be.

However, our nutritional assessment showed that more than half of the newborns were underweight at the first consultation and 70% of the older patients were eutrophic, which may be due to the fact that the most severe heart diseases were referred to the outpatient service at a younger age and with greater nutritional impairment. Surgical intervention resulted in higher mortality in patients with lower weight, but the age at surgical intervention was not a determining factor in mortality.

Despite the similar proportion between female and male patients, our study showed that the outcome of death prevailed in female patients with 26.58%, in contrast to 13.33% of male patients, with no statistical difference. Although the distribution of CHD between the sexes did not show a statistical difference, females presented more total AVSD than males, which may perhaps explain the earlier presentation of these patients to the outpatient clinic, with more advanced conditions and therefore with a difference in mortality, even without statistical confirmation with a $p < 0.05$.

The univariate and multivariate logistic regression model shows CHD TAVSD as an isolated risk factor for death. Other CHDs, even when associated with other comorbidities, do not pose a risk for death.

The lack of universal access to echocardiographic assessment and qualified prenatal care in Brazil makes it difficult to plan births in specialized hospitals that allow immediate cardiological care and the performance of possible intrauterine procedures, such as interventional catheterization[12]. The world literature shows an increasing trend in performing surgical interventions on younger, lower weight patients[8,12]. Thus, late detection of CHD, frequently observed in Brazil, ends up limiting clinical and surgical approaches and impairing the evolution and prognosis of these children.

The average maternal age in our study was 31 years, with a chance of having a child with Down syndrome of approximately (1:900)[3,17].

CONCLUSION

According to the main data in the literature, AVSD is the most common CHD found in the population with DS, with TAVSD being the most frequent.

With this study, we were able to verify data that demonstrated an association with mortality, among them: TAVSD (with a predominance in females, whose group presented almost twice the mortality rate) and surgical weight (the lower the weight, the higher the mortality rate). There was no association of the other comorbidities with the outcome of death.

LIMITATIONS OF THE STUDY

This is a study carried out through the consultation of medical records with the need for access to physical and electronic medical records, with the possibility that certain data may not be adequately recorded in the medical records.

There was a loss of follow-up of approximately 46% of the patients, making it impossible to better assess the evolution of this group of patients.

Patients followed up on an outpatient basis were evaluated and patients who were born with neonatal pathologies or severe malformations that resulted in death and were not evaluated in the outpatient clinic were not considered.

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