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ORIGINAL ARTICLE

Congenital Cardiac Anomalies: The Most Common Anomaly in Children with Down Syndrome

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Abstract

Introduction: Down syndrome (DS) is the most common genetic disorder. Congenital cardiac anomalies are common and are a major cause of mortality and morbidity in cases with DS. The aim of this study was to determine congenital cardiac anomalies in children with DS and to identify the severity of these pathologies.

Methods: Genetically and clinically diagnosed DS cases with congenital cardiac anomalies, whose examination and follow-ups were done in our pediatric cardiology outward clinic between February 1, 2018 and February 1, 2021, were retrospectively reviewed from medical records.

Results: This study consisted of 131 cases with DS, including 72 (54.9%) boys and 59 (45.1%) girls. There were no anomalies in the echocardiographic findings of 54 (41.2%) of the cases. Congenital cardiac anomaly was identified in 77 (58.8%) cases. Of these cases, 10.7% had atrioventricular septal defect, 14.5% had ventricular septal defect, 9.7% had atrial septal defect, 5.3% had patent ductus arteriosus, and 2.3% had tetralogy of fallot and the rest had other pathologies. Surgical treatment was administered to 31 (23.2%) cases. Three cases had pulmonary hypertension. Two cases were administered pacemaker implantation in the postoperative period. Wolf-Parkinson-White syndrome was observed in the electrocardiography of 3 (2.3%) cases. When the cases' other system pathologies were examined, it was observed that 30 cases (22.9%) had hypothyroid, the most common pathology.

Discussion and Conclusion: Half of the patients with DS in the study group had congenital cardiac anomalies. About half of these cases required surgical or invasive intervention. This indicates that cardiac examination and follow-up of patients with DS is important and necessary.

Keywords: Congenital cardiac anomaly; down syndrome; trisomy 21.

In 1959, Lejeune et al. discovered that Down syndrome (DS) is caused by the presence of an extra copy of chromosome 21, also known as trisomy 21[1,2]. DS is the most common genetic syndrome and occurs in approximately 1 in every 650–1000 births[3].

DS is associated with many congenital pathologies. Congenital cardiac anomalies have been reported in patients with DS at a rate of 40–60% and are the major causes of mortality and morbidity in the DS population[1,4,5]. In DS, the rate of mortality is reported as 13% in childhood and

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23% in adulthood[6]. Congenital cardiac anomalies are the most significant causes of these high rates of mortality in patients with DS[6]. However, thanks to medical breakthroughs and improvements in diagnosis and treatment methods, the average life expectancy of these patients has increased from 12 years to 60 years since 1940[3]. Despite this increase in life expectancy, cardiac problems still remain a significant problem for patients with DS.

The aim of this study was to determine congenital cardiac anomalies in children with DS who applied to the pediatric cardiology outward clinic with different health problems and to identify the severity of these pathologies.

Materials and Methods

This study was conducted with patients with DS (Trisomy 21) who were clinically and genetically diagnosed during a 3-year period between January 2, 2018 and January 2, 2021. The cases diagnosed with DS according to the ICD-10 code were reviewed retrospectively from medical records. For the patients who were examined more than once, the latest electrocardiography and echocardiography findings were used.

The severity of congenital cardiac pathologies of the cases was evaluated based on surgical and invasive procedures that were performed, and the presence of pulmonary hypertension and rhythm disturbances. Approval for the study was obtained from the Zeynep Kamil Women's and Children's Disease Training and Research Hospital Ethics Committee and the Scientific Commission in the Directorate of Health Services. All the statistical analysis was done in IBM SPSS 21.0 software. Pearson's Chi-square test was used to find the association between heart anomaly and sex. The significance level used was 0.05 ($p<0.05$). The results are given as mean±standard deviation for all the continuous variables and frequency for categorical variables.

Results

The study group consisted of a total of 131 cases of DS, including 72 (54.9%) boys and 59 (45.1%) girls. The ages of the cases during examination ranged from 1 day to 16 years and 3 months, with an average of 2.88 ± 3.71 years. Table 1 shows the variation of congenital cardiac anomalies of the cases by gender. There was a significant difference between cardiac anomaly and gender, according to the Pearson's Chi-square test ($p=0.002$). No anomalies were found in the echocardiograms of 41.2% of the cases. Table 2 shows the distribution of cardiac pathologies in the cases.

Table 1. Distribution of congenital heart anomalies according to gender

	with CHD	%	without CHD	%	Total	%
Male	32	24.4	40	30.5	72	54.9
Female	45	34.4	14	10.7	59	46.1
Total	77		54		131	100

CHD: Congenital heart diseases.

Table 2. Types of congenital cardiac anomalies distributed by gender

Pathology	Female	Male	Total (n)	(%)
Normal/PFO	14	40	54	41.2
AVSD	9	5	14	10.7
ASD	4	8	12	9.7
VSD	10	9	19	14.5
PDA	5	2	7	5.3
ASD+PDA	2		2	1.5
ASD+VSD	6	3	9	6.8
VSD+PDA	3	1	4	3.0
Fallot	1	2	3	2.3
AVSD+Fallot	1		1	0.7
Hypoplastic LV+CoA	1		1	0.7
Double aortic arch	1		1	0.7
AI	2	2	1.5	
MI	1	1	0.7	
PSSVC	1		1	0.7

PFO: Patent foramen ovale; AVSD: Atrioventricular septal defect; ASD: Atrial septal defect; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; LV: Left ventricule; AI: Aortic valve insufficiency; MI: Mitral valve insufficiency.

Of 31 (23.4%) cases receiving surgical treatment, 29 cases had total repair surgery, 1 case shunt and Glenn operation, and 1 case patent ductus arteriosus (PDA) ligation. 2 (1.5%) cases underwent catheter-based PDA closure procedure. Table 3 shows the surgical procedures performed on the cases. The pathologies of 22 (16.8%) cases required follow-up and intervention. Small defects in 6 (4.5%) cases disappeared spontaneously during follow-up. In the rest of the cases, minor pathologies that only required follow-up without any intervention were observed.

three cases received pulmonary hypertension treatment. In one of the cases, pulmonary hypertension developed post-operation. In another case, the underlying cause was a non-repaired ventricular septal defect (VSD). Finally, in the third, pulmonary hypertension developed without the presence of any related pathologies or underlying causes.

Table 3. Types of surgical treatment applied distributed by gender

Type of surgery	Female	Male	Total (n)	%
VSD repair±PDA ligation	11	1	12	9.1
AVSD total repair	8	5	13	9.9
Glenn operation	1		1	0.7
Fallot total repair	1	2	3	2.3
PDA ligation		1	1	0.7
Aortic arch repair	1		1	0.7

AVSD: Atrioventricular septal defect; ASD: Atrial septal defect; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus.

Wolf-Parkinson-White (WPW) syndrome was observed in the electrocardiography of 3 (2.3%) cases. There were no complaints in two cases, while supraventricular tachycardia developed during medication for attention deficit disorder in one case. Pacemaker implantation was performed on two of these three cases due to the development of atrioventricular (AV) block in the postoperative period.

Thirty cases (22.9%) received treatment for hypothyroidism. No significant difference was found between cardiac anomaly and hypothyroidism according to the Pearson's Chi-square test results (p=0.802). The distribution of hypothyroidism and congenital cardiac anomalies is given in Table 4.

Discussion

Different prevalence rates of DS have been reported in various studies conducted in different time periods and populations[7,8]. The United States Centers for Disease Control and Prevention reported that the incidence of DS in 2006 was 1 in 733 live births[1]. However, the presence of trisomy in 16–18% of miscarriages and postpartum deaths indicates that this ratio is, in fact, higher[1]. In Europe, while the total prevalence of DS was 23.96 per 10,000 births during 2011–2015; when only live births were evaluated, it was 13.69/10,000 live births,[9] EUROCAT 2018. Factors such as

Table 4. Distribution of hypothyroidism and congenital cardiac anomalies

Hypothyroidism	With CHD	%	Without CHD	%	Total	%
Yes	18	13.8	12	9.1	30	22.9
No	58	44.3	43	32.8	101	77.1
Total	76	58.1	55	41.9	131	100

CHD: Congenital heart diseases.

followed-up prenatal diagnosis, approach to termination of pregnancy, differences in gestational age play a role in the difference in prevalence in different countries[8,9]. It was reported that the improvements in treatment opportunities over the years reduced mortality rates[10].

Given that individuals with DS are prone to both congenital and acquired cardiac diseases, and pulmonary hypertension, the examination of cardiac anomalies is crucial in this patient group. Routine examinations and electrocardiogram were reported to remain insufficient for the diagnosis of congenital cardiac anomalies[11]. A study has shown that cardiovascular abnormalities could not be diagnosed in 34% of the examined babies with DS at 6 weeks, and in 24% of the babies at 12 weeks[11]. Hence, in such cases, it is recommended that echocardiography should be done even if the cardiac examination results were found to be normal in the first few weeks[11].

Studies conducted on patients with DS have suggested different prevalence rates for the various congenital heart anomalies observed. In a study conducted over a 22-year period (1985–2006), Irwing et al. have found that the rate of DS was 1.09 per 1000 live births and of these cases, 42% had cardiovascular anomalies. AVSD (37%), VSD (31%), atrial septal defect (ASD) (15%), partial AVSD (6%), Tetralogy of Fallot (TOF) (5%), PDA (4%) and miscellaneous group (including coarctation of the aorta [CoA], pulmonary valve stenosis and vascular ring) (2%) and multiple pathologies (28%) were observed among these pathologies[2]. In a cohort study carried out in the United States, it was determined that 6% of the cases had complex congenital heart disease anomaly (CHD), 22% had AVSD, 22% had VSD and 4% had TOF[12]. Stoll et al. determined the rate of AVSD as 30%, ASD 25%, VSD 22%, PDA 5%, CoA 5%, TOF 3% and other CHD 9%[7]. In our study, we have observed congenital cardiac anomaly in 58.8% of the cases. Of these cases in question, 10.7% had AVSD, 14.5% had VSD, 9.7% had ASD, 5.3% had PDA and 2.3% had TOF and the rest had other pathologies.

The study group of the cohort study conducted in the United States was composed of 46% girls and 52% boys[13]. Of the DS case group in our study, 46.1% were girls and 53.9% were boys. In the literature, it is stated that congenital cardiac diseases are more common in females[8]. Similarly, in our study group, it was observed that congenital cardiac anomaly was higher in females. The congenital heart anomaly rate was 24.4% in males, whereas 34.4% in females. In the study of Santaro et al.[8] and the meta-analysis of Diogenes et al.,[14] it was reported that CHD, par-

ticularly AVSD, and TOF are more common in the females with DS[14]. In our study, AVSD was more common in the females. In terms of TOF, two of the cases diagnosed with fallot were male and one was female. The case with AVSD and TOF was also a female.

Thirty of 77 cases required surgical intervention. Some of these cases required surgical intervention during the follow-up period. In their study carried out in 63 centers, Fudge et al. have reported that patients with DS did not have a significantly higher mortality risk in the postoperative period compared to patients without DS, while the postoperative process appears to have prolonged in patients with DS compared to patients without DS[4]. The rates of pacemaker implantations were higher in these cases thus; the development of postoperative AV block and pacemaker requirement observed in our cases may be related to this. However, no relationship between DS and WPW was mentioned. We do not have any information about the WPW syndrome and the difference in the prevalence of WPW syndrome in individuals with and without DS. Differences in AV node development in DS patients with AVSD and normal hearts play a role in postoperative and non-operative cardiac conduction disorders in DS cases[15]. In their study carried out with 197 cases whose mean age was 31 (21.1–60.5) years, Hayes et al. reported that residual cardiac damage continued in 67% of 127 cases despite receiving surgical intervention, while 28% had arrhythmia[13]. In our study group, residual defects in the patients who underwent surgery were not serious. The observed ongoing problems were valve regurgitations, minor residual defects, etc. In the literature, it is stated that valve regurgitation may develop in normal children as well[11]. Among our cases, there were elder children who developed mild aortic and mitral valve regurgitation without any other accompanying cardiac anomalies.

Pulmonary hypertension is known to be very common in DS patients[16]. The majority are associated with severe CHD. Resistant hypertension, which is observed in patients who do not receive treatment at an early phase, was observed in one of our cases, and treatment for resistant pulmonary hypertension was administered. In such cases, postoperative pulmonary hypertension may develop even when early surgical intervention is performed. In addition, pulmonary hypertension may develop in DS cases without cardiac pathology due to the presence of other diseases such as obstructive sleep apnea, hypoxia, and recurrent pneumonia,[16] as well as other acquired cardiac pathologies later on during adulthood,[15] making the follow-up of these cases for cardiac problems necessary.

Conclusions

In conclusion, although prenatal diagnostic methods have improved, the chance of having a child with DS varies among populations due to cultural differences. As the relationship between congenital cardiac anomalies and this syndrome is becoming well known, the rates and accuracies of diagnoses have significantly improved. However, despite the early diagnosis and treatment of these anomalies, problems related to congenital cardiac anomalies still remain an important problem. In addition, the possibility of the development of pathologies such as pulmonary hypertension, valve regurgitation, and arrhythmia, even in patients who have received treatment and show no signs of residual pathologies, emphasizes the importance of cardiac examinations in the follow-up of patients with DS and the presence of other comorbid non-cardiac congenital anomalies reveal the necessity of multidisciplinary follow-ups and studies.

Limitations

Since our study did not include all DS cases who were prenatally diagnosed, live births of stillbirths, it does not accurately reflect the prevalence of DS and the rate of congenital anomalies. However, despite the limitations, our study is significant as it demonstrates children with DS from different age groups and their cardiac anomalies.

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