ORIGINAL ARTICLE

CO-OCCURRING CONGENITAL HEART DEFECTS IN TRISOMY-21/ DOWN SYNDROME: A CROSS-SECTIONAL STUDY IN A TERTIARY CARE HOSPITAL, PAKISTAN

Qazi Muhammad Maaz[1], Farhat Ullah Jan[1], Mashal Khan[2], Salman Mustaan Khan[3], Ayesha[1], Savaira Elahi[2], Kainat[1]

[1]Department of Pediatrics, Hayatabad Medical Complex, Peshawar - Pakistan

[2]Department of General Surgery, Hayatabad Medical Complex, Peshawar - Pakistan

[3]Department of Pediatrics, Saidu Teaching Hospital, Swat - Pakistan

ABSTRACT

OBJECTIVE: This study aimed to determine the frequency of Congenital heart disease CHD and its types in children with Down syndrome DS admitted to a tertiary care hospital in Peshawar, Pakistan.

MATERIAL & METHODS: This descriptive cross-sectional study was conducted from August 2023 to February 2024 in the Department of Pediatrics and Pediatric Cardiology, Hayatabad Medical Complex (HMC), Peshawar. A sample size of 135 was obtained. A non-probability consecutive sampling technique was used to select patients. All admissions of DS, irrespective of the reason for admission, were confirmed by the presence of phenotypic features. CHDs were diagnosed via transthoracic echocardiography.

RESULTS: The mean age of the patients was 7±5.19 years. Sixty-three (46.7%) were males and 72 (53.3%) were females. The occurrence of CHD among DS patients was 85 (63.0%), of which 69 (81.2%) were acyanotic and 16 (18.8%) were cyanotic heart diseases. The most common types of CHDs were VSD (28, 32.9%) and PDA (19, 22.4%), followed by ASD (11, 12.9%) and AVSD (11, 12.9%). No significant difference was noticed for CHDs or types of CHDs across age, gender, and residence groups ($p>0.05$).

CONCLUSION: Our study concludes that almost two-thirds of the DS patients had CHDs, among which VSDs, PDAs, ASDs, and AVSDs were the most common. It underscores the importance of early screening for cardiac anomalies so that prompt interventions are provided in time for improving healthcare outcomes among this population group.

KEYWORDS: Down syndrome, Congenital heart defects, Heart abnormalities, Ventricular septal defect.

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INTRODUCTION

Down syndrome (DS) is one of the most common chromosomal disorders characterized by a distinct group of phenotypic features. It commonly manifests with features like mental disability, developmental delay, facial features, cardiac abnormalities, hypotonia, etc., in infancy. [1] Worldwide, it has an estimated frequency of 1 per 600 to 1 per 1000 live births, making it a major public health concern with lifelong social, medical, and economic implications for the affected families and healthcare systems.[2]

The underlying defect in DS results from complete or partial trisomy of chromosome 21, which may occur through nondisjunction, Robertsonian translocation, or mosaicism during meiosis of germ cells. [3, 4] Among the risk factors, advanced maternal age is considered the most important for DS. [5] Other risk factors like parental health, family history, geographic, and environmental influences have also been recognized. Data are scarce about the exact figure of its prevalence in Pakistan. However, a local study reported that 1 in 300 births in Pakistan are affected by DS, which is almost double compared to other parts of the world. [6]

Features of DS are diverse and may manifest in nearly every organ system, ranging from craniofacial fea-

Correspondence
Dr. Mashal Khan
House Officer
Department of Surgery, Hayatabad Medical Complex,
Peshawar - Pakistan
Cell. +92-312-9037258
Email: mashal.khan@kmc.edu.pk
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tures and musculoskeletal abnormalities to neurological, gastrointestinal, and hematological disorders. [7] Among these, congenital heart defect (CHD) is the most common condition of the cardiovascular system in this group and plays a major role in their early survival and quality of life. The prevalence of CHD has been reported by many studies with varying frequencies, such as 50%, 66%, and 96%.[2, 3, 8] The common type of cardiac defect varies across different regions. In the United States (US) and Europe, atrioventricular septal defects (AVSD) are found to be the most common, while in Asian countries, ventricular septal defects (VSD) are prevalent, and in Latin America and Korea, atrial septal defects (ASD) are the most common. [9] CHD is the primary cause of morbidity and mortality in the first two years of their lives. [2]

Nearly 10% of total cardiac surgeries are comprised of DS patients. Beyond the cardiovascular complications, DS is associated with other health challenges, like growth and development. Growth failure becomes even more pronounced when CHD coexists, leading to poor weight gain, delayed milestones, and vulnerability to infection. [10]

The prevalence and type of CHD vary across different populations. This study aimed to determine the frequency of CHD and its types in children with Down syndrome presenting to Hayatabad Medical Complex, Peshawar, which is one of the 3 tertiary care hospitals in the city.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted from August 2023 to February 2024 in the Department of Pediatrics and Pediatric Cardiology, Hayatabad Medical Complex (HMC), Peshawar. HMC, located in the suburb of Peshawar, located in the suburb of Peshawar, serves as one of the major tertiary care hospitals and referral centers for the Khyber Pakhtunkhwa (KPK) region. Its pediatric cardiology unit specializes in diagnosing and treating congenital and acquired heart conditions in the pediatric population. It is equipped with an electrocardiogram (ECG), echocardiogram (ECHO) (fetal, transthoracic, and transesophageal), cardiac computed tomography (CT) scan, cardiac magnetic resonance imaging (MRI) scan, and stress tests. Heart repair surgeries are provided here for CHDs. Ethical approval for this study was obtained from the Institutional Research and Ethical Review Board (IREB) of HMC (Approval number: 1422). STROBE guidelines are followed to report the study results.

The Sample size was calculated using the World Health Organization (WHO) calculator. [11] Keeping a 95% confidence level, 8% margin of error, and 66% expected frequency of CHD in the DS population, a sample size of 135 was obtained as given below:

$N = Z^2\, p\,(1-p)/e^2$

Confidence level = 95% → $Z = 1.96$

Expected prevalence, p = 66% → $p = 0.66$

Margin of error, e = 8% → $e = 0.08$

Based on the formula:

$N = 1.96^2 \times 0.66 \times (1-0.66)/0.08^2 \rightarrow N = 134.70$

Participants were recruited through a non-probability consecutive sampling technique till the required sample size was achieved. All admissions of DS, irrespective of the reason for admission, were considered. Patients of both genders and ages 1 month to 16 years were included.

DS was confirmed by the presence of phenotypic features like mongoloid facies, depressed nasal bridge, protruding tongue, low-set ears, upward slanting eyes, medial epicanthic folds, brachycephaly, short neck, short and broad hands, simian crease, clinodactyly, hypotonia, delayed milestones, etc., by two independent pediatricians. Due to the high cost of karyotyping, it was not performed on all patients. Patients with unwilling parents, diagnostic uncertainty, and CHD due to other syndromic conditions were excluded. Patients fulfilling the inclusion criteria were enrolled from the Pediatric ward of HMC Peshawar.

Written informed consent was taken from parents after explaining the purpose of the study. Data was entered in a specially designed proforma. Demographic data, including age, gender, and residence, were noted. A complete history was taken, and a physical examination was done. All children underwent a 2-dimensional transthoracic echocardiographic assessment, aided by Doppler and Color flow mapping, irrespective of the presenting complaint. The equipment used was a Philips iE33 ultrasound system (Philips Medical Systems, Bothell, WA, USA), operated by pediatricians. The ECHOs were observed and reported by two pediatricians and later on further examined by a pediatric cardiology specialist to ensure certainty and consistency. Any single or co-existing defects of the heart structure and the major blood vessels were interpreted as CHDs.

Data was entered and analyzed by using IBM SPSS Statistics v24 software (IBM Corp, Armonk, NY, USA). Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were calculated for categorical variables. Effect modifiers like age, gender, and residence were addressed through the stratification of data against the presence of CHD. Post-stratification chi-square test was applied. P-value ≤ 0.05 was taken as

statistically significant.

RESULTS

The demographic data of the DS patients in the study population are given in Table 1. The mean age of the patients was 7±5.19 years, while the median age was 6.2 years (IQR: 3.4-10.8), suggesting a slightly right-skewed distribution. With respect to gender, 63 (46.7%) were males and 72 (53.3%) were females, showing a slight predominance in our cohort. Overall, the occurrence of CHD among DS patients was 85 (63.0%). Among these, 69 (81.2%) were in the category of acyanotic and 16 (18.8%) were in the category of cyanotic heart diseases.

The prevalence of different types of CHDs observed in our study population is summarized in Table 2. Among these, VSD was the most common lesion identified, affecting 28 (32.9%) patients. The second most common was PDA, which was observed in 19 (22.4%) patients. ASD and AVSD were each diagnosed in 11 (12.9%) patients, representing a smaller but notable proportion of cases. Table 3 shows the stratification of CHD concerning age, gender, and residence. Although no significant difference was noticed among groups (P > 0.05), certain trends were observed. The prevalence was higher among the age group 1 month-7 years, affecting 65.6% patients, among males, affecting 66.7%, and among urban residents, affecting 66.7%.

Stratification of types of CHD across age groups, gender, and residence is given in Table 4. There were no

Table No 1: Demographic Data Of The Patients (N=135)

VARIABLES	N (%)
AGE	
1 month-7 years	96 (71.1)
8-16 years	39 (28.9)
GENDER	
Male	63 (46.7)
Female	72 (53.3)
RESIDENCE	
Urban	57 (42.2)
Rural	78 (57.8)

Table No 2: Distribution Of Types Of Congenital Heart Defects (N=85)

TYPES OF CONGENITAL HEART DEFECTS	N (%)
Ventricular septal defect	28 (32.9)
Patent ductus arteriosus	19 (22.4)
Atrial septal defect	11 (12.9)
Atrioventricular septal defect	11 (12.9)
Teratology of Fallot	9 (10.6)
Pulmonary atresia	4 (4.7)
Complex cardiac lesion	3 (3.5)

Table No 3: Stratification Of Congenital Heart Defect Concerning Age, Gender, And Residence (N=135)

	CONGENITAL HEART DEFECT		P-VALUE
	YES, N (%)	NO, N (%)	
AGE			
1 month-7 years (n=96)	63 (65.6)	33 (34.4)	0.31
8-16 years (39)	22 (56.4)	17 (43.6)	
GENDER			
Male (n=63)	42 (66.7)	21 (33.3)	0.40
Female (n=72)	43 (59.7)	29 (40.3)	
RESIDENCE			
Urban (n=57)	38 (66.7)	19 (33.3)	0.45
Rural (n=78)	47 (60.3)	31 (39.7)	

Table No 4: Stratification Of Types Of Chds Concerning Age, Gender, And Residence (N=85)

	TYPES OF CHDS, N (%)							P-VALUE
	VSD	PDA	ASD	AVSD	TOF	PA	CCL	
AGE								
1 month-7 years (n=63)	20 (31.7)	13 (20.6)	9 (14.3)	8 (12.7)	7 (11.1)	3 (4.8)	3 (4.8)	0.85
8-16 years (n=22)	6 (27.3)	4 (18.2)	4 (18.2)	2 (9.0)	4 (18.2)	2 (9.0)	0 (0.0)	
GENDER								
Male (n=42)	14 (33.3)	9 (21.4)	7 (16.7)	5 (11.9)	5 (11.9)	1 (2.4)	1 (2.4)	0.98
Female (n=43)	14 (32.6)	10 (23.3)	5 (11.6)	7 (16.3)	4 (9.3)	2 (4.6)	1 (2.3)	
RESIDENCE								
Urban (n=38)	12 (31.6)	9 (23.7)	4 (10.5)	4 (10.5)	6 (15.8)	2 (5.3)	1 (2.6)	0.99
Rural (n=47)	16 (34.0)	10 (21.3)	6 (12.8)	6 (12.8)	5 (10.6)	3 (6.4)	1 (2.1)	

CHD=Congenital heart defect, VSD=Ventricular septal defect, PDA=Patent ductus arteriosus, ASD=Atrial septal defect, AVSD=Atrioventricular septal defect, TOF=Teratology of Fallot, PA=Pulmonary atresia, CCL=Complex cardiac lesion

significant differences among all groups regarding the prevalence of the specific types of CHD (P > 0.05). But noteworthy, some patterns were observed when the data was examined by gender. Among males, VSD (33.3%) was the commonest, followed by PDA (21.4%) and ASD (16.7%). Among females, VSD (32.6%) remained the commonest, but was followed by PDA (23.3%), and AVSD (16.3%).

DISCUSSION

Our study demonstrates a 63.0% prevalence of CHD among DS patients. Certain variations exist among different national and international studies regarding their prevalence.

However, the majority of them suggest a higher rate of occurrence of CHD among DS patients. Yaqoob M et al. reported a prevalence of 41.8% in Lahore[12], Afzal E et al. reported 48.0% prevalence in Multan[13], and Khan I et al. reported 56.4% prevalence in Peshawar.[14] Studies in other countries like Saudi Arabia[2], Nigeria[3], India[15], and the United States[16], have reported prevalence of 66%, 95.8%, 50.0%, and 59%, respectively. Potential factors like demographic features, sample sizes, diagnostic tools, screening protocols, genetic factors, and consanguinity could lead to these discrepancies in prevalence across different regions. However, almost all these studies establish CHD as a major comorbidity in DS.

Our results illustrate that pediatricians are more likely to encounter acyanotic defects (81.2%) as compared to cyanotic defects (18.8%) among DS patients. Our findings in this regard align with previous studies conducted by Bilal A et al. [17] and Rehman Y et al. [10,] who observed 80.8% and 82.1% acyanotic, and 19.2% and 17.8% cyanotic defects among the studied DS cohorts. It could be due to the reason that the genetic defects of trisomy-21 affect the early stages of cardiac development, leading to endocardial cushion defects.[18]

Moreover, our study found a slightly higher number of male patients (66.7%) to have CHDs than females (46.7%). Haider A et al. have found that females are more prone (OR=1.72) to experience cardiac involvement compared to males. [19] Other studies have also established the same conclusions. [20]

This observation raises the possibility of gender predisposition to cardiac anomalies. While the exact mechanism remains uncertain, some authors suggest that the role of X-linked gene expression and sex hormones might be at play, which influence cardiac development.

Our findings indicate the most common type of CHD among the studied cohort was VSD (32.9%). It was followed by PDA (22.4%), ASD (12.9%), and AVSD (12.9%). Our observations and previous studies are largely consistent regarding the prevalence of common types of CHDs in DS, with minor differences. A study in Lahore found VSD as the most prevalent (46.2%), followed by AVSD (26.9%), and TOF (15.4%). [17] This is further corroborated by other studies where VSD was found as the commonest CHD with 22.3% [10] and 41.0% [12] prevalence. A comparative study at Aga Khan University found AVSD with the highest prevalence (67.0%) and VSD as the second highest (22%). [21] Similarly, there are other studies establishing AVSD as the more common type than VSD alone. [3] Another previous study has found AVSD (36.1%), VSD (30.5%), and ASD (25.0%) as the common CHDs among DS patients. [22] These variations in the distribution of CHD subtypes may be related to genetic background, environmental influences, or methodological differences across studies. Such discrepancies highlight the importance of generating population-specific data, as the prevalence of CHDs among DS does not appear to be uniform across different settings.

Although gender predispositions for specific types of CHD have been reported in earlier studies [19], we did not observe any findings that could support such an association (p=0.98). This can be explained by the fact that such variations among genders are very subtle and, if present, may require a larger sample size. Despite our negative findings, the role of gender in the spectrum of CHDs remains an important area for future studies.

Our study has several limitations. A smaller sample size and single-centered nature could affect the generalization of the findings to all Down syndrome population. Additionally, the diagnosis of DS was based on clinical findings rather than genetic karyotyping due to financial constraints for the research, which would have made it more reliable.

CONCLUSION

Our study concludes that almost two-thirds of the DS patients had CHDs, among which VSDs, PDAs, ASDs, and AVSDs were the most common. Other regions have reported AVSD or PDA as the most common, VSD being the most common in our study, suggesting a possible geographic or genetic variability in this spectrum of

population, which needs multicenter and genetic studies for further confirmation. Our findings also highlight the disease burden in our population and reinforce the standard protocol of early screening in DS patients for cardiac anomalies. It will help to take prompt interventions on time for enhanced healthcare outcomes among this population group.

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Authors Contribution:

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Maaz QM	✓	×	✓	×	×	✓
Jan FU	✓	✓	×	✓	✓	×
Khan M	✓	×	✓	×	×	✓
Khan SM	✓	✓	×	×	✓	×
Ayesha	✓	×	✓	×	×	✓
Elahi S	✓	✓	×	✓	✓	×
Kainat	✓	×	✓	×	×	✓

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval:

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