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SPECTRUM OF CONGENITAL HEART DISEASE IN DOWN SYNDROME AT FAISALABAD INSTITUTE OF CARDIOLOGY: A RETROSPECTIVE STUDY.

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ABSTRACT: Congenital heart disease (CHD) is the most common structural anomaly in Down syndrome children with a variable spectrum all over the world including Pakistan. **Objectives:** To determine the spectrum of congenital heart disease in Down syndrome at Faisalabad Institute of Cardiology (FIC) Faisalabad. **Study Design:** Retrospective descriptive case series. **Setting:** Paediatric Cardiology Department of FIC, Faisalabad. **Period:** From January 2013 to June 2019. **Material & Methods:** All consecutive patients of Down syndrome who underwent diagnostic Echocardiography at FIC were enrolled. Those having confirmed diagnosis of CHD were included in the study. **Results:** Out of 321Down syndrome children77.6% (n=249) had CHD and were enrolled for study. Male were 53.8% (n=134) while 46.2% were female (n=115). Majority of patients were below one year of age (57%, n=142). Acyanotic CHD was seen in 83.1 % of patients (n=207) while 16.9 % (n=42) had cyanotic CHD. Isolated cardiac defects were seen in 73.1% of patients (n=182) while 26.9 % had mixed cardiac lesions (n=67). Ventricular septal defect (VSD) was the most common (22.1%, n=55) solitary lesion followed by 14.5% cases of atrioventricular septal defect (AVSD), PDA (13.3%) and ASD (8.8%). Tetralogy of Fallot (TOF) was seen in 8.4%, AS in 1.2% while TGA, Tricuspid atresia, pulmonary valve stenosis, coarctation and Ebstein anomaly (0.8% each) were less common solitary defects. In mixed cardiac defects VSD with PDA was the most common (n=13, 5.22%) followed by VSD with ASD (n=12, 4.81%) and VSD with RVOTO (n=8, 3.21%). In AVSD cases, RVOTO was present in 2.81% (n=7), PDA with ASD was seen in 2% cases (n=5) while ccTGA, DORV and Pulmonary atresia (PA) were least common. Pulmonary hypertension was present in 54.2% cases of left to right shunt lesions. **Conclusion:** Incidence of CHD in referred cases of Down syndrome is high (77.6%) at our setup. Acyanotic congenital heart defects are more common. VSD is the most common acyanotic CHD followed by AVSD while TOF is the most common cyanotic CHD.

Key words: Congenital heart disease, Down syndrome, Pulmonary hypertension, Tetralogy of Fallot, Ventricular septal defect.

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INTRODUCTION

Down syndrome (DS) is a genetic defect which usually can result in significant medical morbidity in the affected children, especially congenital heart defect (CHD).[1] The prevalence of DS is approximately one in 700 live births[2] while the reported incidence of CHD in Down syndrome is 40 to 60%.[3]

The spectrum of CHD in Down syndrome varies world wide depending upon geographic, socio-demographic and genetic factors.[4] The most common forms of CHD reported in children with DS, in descending order, are Atrioventricular septal defect (AVSD), Ventricular septal defect (VSD) and Atrial septal defect (ASD).[5] Septal defects are high in number but there are lower rates of other conotruncal defects like Tetralogy of Fallot (TOF) and Transposition of great arteries (TGA) or conditions such as Coarctation of aorta (CoA).[6]

Failure to recognize cardiac defects early in life can have serious consequences including establishment of pulmonary hypertension (PH). The presentation of DS with irreversible pulmonary

artery disease indicates that importance of early detection is not fully acknowledged, even in the present era.[2,7]

Echocardiography is an easy non-invasive procedure to diagnose CHD. Pakistan is a developing country where children born as DS are either not diagnosed for this genetic defect and if diagnosed on clinical basis are not referred in time for CHD screening. By knowing the spectrum of various congenital heart diseases in Down syndrome we can plan early surgery in high risk patients to decrease the mortality and morbidity. The aim of the study was to determine the spectrum of congenital heart defects in Down syndrome children presenting at Faisalabad Institute of Cardiology (FIC) Faisalabad.

MATERIAL & METHODS

It was a descriptive retrospective case series conducted at paediatric cardiology department of FIC. Three hundred and twenty one consecutive patients of Down syndrome who presented at FIC and underwent echocardiography by dedicated paediatric cardiologist of the Institute from January 2013 to June 2019 were enrolled in the study. Approval from ethics committee of the hospital was obtained and there was no conflict of interest. Patients of any gender or age diagnosed by a referring paediatrician as Down syndrome on pheno-typical features, counter checked by the principal investigator and then diagnosed as having CHD on echocardiography were included.

The patients presenting in output patient department (OPD) or admitted in the hospital through emergency for possible diagnosis and management of CHD including medical management, cardiac surgery, cardiac catheterization or any catheter based intervention were included. Those who had dysmorphism with CHD other than Down syndrome, who already had been operated for CHD (whether palliated or completely repaired) or already had device or balloon intervention done, those having Patent foramen ovale (PFO) or isolated bicuspid aortic valve with normal valve function and those having acquired heart defects like myocarditis with left ventricular (LV) dysfunction or cardiomyopathy were excluded. The records were retrieved and reviewed by the principal investigator for presence or absence of congenital heart disease in such patients.

Demographic data including patient name, age, gender (male/ Female/ Transgender), hospital registration number, contact number (mobile as well as landline) and area of residence were noted. Clinical parameters like weight in kilograms (Kg) and cutaneous saturation by pulse oximetry (SpO_2) was noted. Anatomical diagnosis of the congenital heart defect was noted followed by type of CHD like cyanotic, acyanotic, isolated CHD or additional associated cardiac defects present with main heart defect, presence or absence of pulmonary hypertension or pericardial effusion was also noted. The required variables were entered into an investigator-designed Proforma. The collected data was analyzed. The mean and the standard deviations were calculated for the quantitative variables like age and weight. The frequencies and percentages were calculated for qualitative variables like gender, anatomical diagnosis and type of congenital heart disease.

RESULTS

Demographics and clinical characteristics

Record of 321 patients of Down syndrome was available and out of which 249 patients had CHD (77.6%) while 72 patients with no CHD were excluded from the study. Out of 249 patients with CHD, 53.8 % were male (n=134) while 46.2% were female (n=115) with male to female ratio of 1.2:1. Majority of patients were below one year of age (57%, n=142) followed by those who were above 1 year of age but below 5 years (28.1%, n=70) while 14.9% (n=37) were above 5 years of age. Mean weight of the patients was 8.8kg. Majority of the children were referred from other hospitals or clinics in OPD (88%, n=219) followed by 8.4% patients admitted through emergency (n=21), while 2.8% were admitted for cardiac surgery (n=7) and only 2 patients (0.8%) were admitted for cardiac catheterization. As regard type of CHD, the majority of patients had acyanotic congenital heart defects (83.1%, n=207) while cyanotic heart diseases were less

common (16.9%, n=42). The demographic and clinical profile of patients is given in Table-I.

Variables	n (%)
Down syndrome patients	321 (100%)
With CHD	249 (77.6%)
Without CHD	72 (22.4%)
Age Groups	
< 1year	142 (57%)
1-5Years	70 (28.1%)
>5years	37(14.9%)
Gender	
Male	134 (53.8%)
Female	115 (46.2%)
Mode of Presentation	
OPD	219(88%)
Emergency	21(8.4%)
Cardiac surgery	07 (2.8%)
Cardiac catheterization	02 (0.8%)
Type of CHD	
Acyanotic CHD	207 (83.1%)
Cyanotic CHD	42(16.9%)
Type of Lesion	
Isolated/solitary lesions	182 (73.1%)
Mixed/associated lesions	67 (26.9%)

Table-I. Demographic Profile and Clinical Characteristics.

Spectrum of CHD

Study population was divided in to those having isolated CHD and those having associated heart defects. Isolated cardiac defects were seen in 73.1% of patients (n=182) while 26.9 % had associated or mixed cardiac defects (n=67).

A). Isolated cardiac defects

Isolated VSD was present in 22.1% of patients (n=55) and was the most common cardiac defect followed by AVSD (14.5%), PDA (13.3%), ASD (8.8%) and TOF (8.4%). The isolated defects with their frequency are shown in Table-II.

B) Associated cardiac defects

These were more commonly seen with VSD (n=35). VSD with PDA was the most common (n=13, 5.22%) followed by VSD with ASD (n=12, 4.81%) and VSD with RVOTO (n=8, 3.21%). As regard AVSD cases, RVOTO was the most common (n=7, 2.81%) associated defect. The frequency of associated mixed lesions is shown in Table-II.

C). Co-morbid cardiac conditions

Out of 202 patients having left to right shunt (Univentricular heart physiology patients included) pulmonary hypertension was the most common co-morbid cardiac condition (n=109, 54.2%). similarly Pericardial effusion was seen in 4% of Down syndrome patients with CHD as shown in Table-III.

Isolated Lesions (n=182, 73.1%)		Mixed Lesions (n=67, 26.9%)			
Lesion	**No. (%)**	**Lesion&%**	**No. (%)**	**Lesion**	**No. (%)**
VSD	55 (22.1%)	VSD+PDA	13 (5.22%)	PA+VSD+ PDA	1 (0.4%)
AVSD	36 (14.5%)	VSD+ASD	12 (4.81%)	UVH+CAVSD+PDA	2(0.8%)
PDA	33 (13.3%)	VSD+PDA+ASD	2(0.8%)	UVH+CAVSD+RVOTO	1(0.4%)
ASD	22 (8.8%)	VSD RVOTO	8 (3.21%)	PA+VSD + ASD	1(0.4%)
TOF	21 (8.4%)	ASD+PDA	1 (0.4%)	Mitral atresia + VSD+PS	1(0.4%)
AS	3 (1.2%)	AVSD+RVOTO	7(2.81%)		
TGA intact IVS	2 (0.8%)	AVSD+ PDA	4(1.60%)		
TA	2(0.8%)	PDA+ASD	5(2.00%)		
PS	2 (0.8%)	PS+ASD	1(0.4%)		
Coarctation of aorta	2(0.8%)	TOF+PDA	3(1.2%)		
Ebstein anomaly	2(0.8%)	TOF+ASD	1(0.4%)		
RVOTO	1(0.4%)	ccTGA + VSD	2(0.8%)		
UVH	1(0.4%)	DORV+VSD+PS	2(0.8%)		

Table-II. Isolated and mixed cardiac defects in Down syndrome.

PDA (Patent ductus arteriosus), ccTGA (Congenitally corrected transposition of great arteries), AS (Aortic valve stenosis), IVS (Interventricular septum), TA (Tricuspid atresia), PS (Pulmonary valve stenosis), RVOTO (Right ventricular out tract obstruction), UVH (Univentricular heart) , PA (Pulmonary atresia), CAVSD (Complete AVSD)

Co-morbid cardiac Condition		Number of cases	Percentages
Pulmonary Hypertension (n=109, 54.2%)	Mild	16	14.7%
	Moderate	13	11.9%
	Severe	80	73.4%
Pericardial Effusion (n=10, 4%)		10	4%

Table-III. Co-morbid cardiac conditions in down syndrome children with CHD.

DISCUSSION

Faisalabad Institute of Cardiology is a tertiary cardiac care institute of Punjab. The paediatric cardiology department is providing diagnostic as well as management facilities to children having CHD. A large population of children is referred for CHD screening. This study is based on the diagnosis of CHD using echocardiography in the referred cases of DS at FIC.

The reported incidence of CHD in Down syndrome in different studies is 40-60%.[8,9,10] In our study the incidence was 77.6% in the referred cases of Down syndrome which is quite high as compared to above mentioned studies but comparable to different studies from Nigeria by Okeniyi JA et al[11] and Asani et al[12] as well as Brazil study[2] where incidence of CHD in Down syndrome was 75.7%, 77.1% and 81.2% respectively. The reason for this high incidence of CHD in Down syndrome is selective referral for screening of CHD in such cases at our setup and we think that still a lot of work to be done to build awareness in paediatricians for screening of CHD in each and every Down syndrome child.

The gender ratio of CHD patients showed male preponderance with male to female ratio as 1.2:1. The findings are consistent with reports from Verma RS et al[13] and Kovaleva et al.[14] Most patients of DS have acyanotic congenital heart defects. A study conducted in Ethiopia[15] showed 93.9% of patients of DS had acyanotic CHD. Our study is not different from international data and 83.1% cases of DS had acyanotic congenital heart defects. As regards spectrum of CHD, there were isolated as well as mixed cardiac defects.

Isolated Cardiac Defects

VSD was the most common isolated CHD seen in 22.1% patients of our study population. The results are comparable to different studies available in Pakistan and countries around. A study conducted in Afghanistan by Sharifi AM et al[16] reported 23% cases of isolated VSD which was also the most common CHD in their study. Similarly in a study by Hyder SN et al[17] in the Children's Hospital Lahore isolated VSD was the most common CHD (60.5%). Other studies from Iran[18] and India[19] also showed similar results. This shows that VSD is the dominant CHD in such children in Pakistan and neighbouring countries.

In our study AVSD is the second most common isolated CHD (14.5%). AVSD has been reported to be the most common congenital heart defect in Down syndrome in different studies from different parts of the world. This variability in type of lesions could be due to ethnic, genetic, geographical and environmental conditions worldwide. In different studies from Asia and other parts of the world VSD is the most common CHD while in others AVSD is the most common. AVSD was the most common CHD seen in 29.9% followed by VSD (21.5%) in a study by Benhaourech S et al[20] conducted in Casablanca. In a study from Algeria by Boussouf K et al[21], the most common CHDs were atrioventricular septal defect, isolated (30%) or combined with other cardiac abnormalities (44%), followed by 17% cases of VSD. Some other studies from Europe and United States of America[22,23] also report AVSD as the most common CHD.

Isolated PDA is the third most common CHD (13.3%) in our study which is comparable to the study conducted in Mexico by Figueroa JR et al[4] and Laursen HB[24] but the total number of cases were very low in both studies i.e. 160 and 80 respectively as compared to our study (249 cases).

In our study ASD secundum is present in 8.8% of DS children with CHD as an isolated lesion. The results are comparable to most of the studies from Europe[25] and America.[26] ASD has been described as the most common CHD in DS patients in a few studies like Elmagrpy Z et al[27] and Figueroa JR,[4] which is not a common happening and most of the studies around the world favour a relatively lower incidence of secundum ASD.

As regard cyanotic CHDs, Tetralogy of Fallot (TOF) is the most common cyanotic CHD seen in 8.4% patients of our study population. This is the most common cyanotic CHD in most of the studies. Okeniyi et al[11] reported incidence of isolated TOF as 7.5% which is comparable to our study. Similarly in a study conducted by Khan I[28] the incidence of isolated TOF was 6.4% but the number of subjects studied were very small in number (31) although it was the most common cyanotic CHD. TOF was present in 16.05 % DS patients and was the most common cyanotic CHD in a study from India by Meshram RM.[29] All these studies conclude that TOF is the most common cyanotic CHD in DS.

The spectrum of CHD also included a few number of complex cardiac lesions for example Ebstein anomaly (0.8%), tricuspid atresia (0.8%) and TGA (0.8%). In a study carried out in Sweden[30] TGA was only 1.9% of the CHD seen in Down syndrome. The incidence of TGA in studies from Lahore[17] and Swat[31] (Pakistan) was 1.7% and 5% respectively while the number of subjects in both studies were only 63 and 20 respectively. In a recent study from Tokyo[32] the reported incidence of Ebstein anomaly and tricuspid atresia is 0.3 % and 0.1% respectively thus comparable to our study. The reason for less number of complex CHDs in down syndrome could be early death in neonatal life or may be during intra-uterine life as such cases have more associated congenital anomalies of other organ system.

Mixed Cardiac Defects

In our study 26.9% of CHD patients had mixed lesions. VSD with PDA (5.22%) was the most common mixed lesion. In Narayanan DL et al[5] study 5.4% cases of VSD with PDA were found as mixed lesions and our study results are comparable. The next most common mixed lesion in our study was VSD with ASD seen in 4.81% cases and the results are almost comparable to Nisli K et al[33] study done in Turkey.

AVSD with RVOTO which is a variant of TOF was seen in a few cases (2.81%) in our study which is comparable to Morsy MM[34] and McElhinney[35] studies each having 2.26% and 2% cases respectively. The other mixed lesions were very low in number like PDA with ASD, TOF with PDA while complex mixed lesions were extremely rare like ccTGA with VSD, DORV with VSD and PS, Pulmonary atresia with VSD and PDA, Univentricular heart with CAVSD and RVOTO.

Co-Morbid Conditions

Development of pulmonary arterial hypertension (PH) is one of the complications of CHD in Down syndrome. A study conducted in India[36] showed 51.4% of Down syndrome patients of left to right shunt had pulmonary hypertension on Echocardiography. Our study was comparable to this study as regard pulmonary hypertension. In our study majority of patients with PH had severe PH (73.4%) which is slightly higher than Mourato FA[2] where 57.1% had severe PH. The reason could be more number of patients studied in our case (202) as compared to their study (112) as regard PH is concerned.

There are a few limitations in our study. We selected patients on pheno-typical criteria as the record of cytogenetic studies was not available in the data base which could be due to a high cost of such studies in a poor country like Pakistan. Secondly the study is not population based and we believe that huge number of Down syndrome children never report for cardiac evaluation and they either die at home or present in general paediatric medicine unit, in a sick condition and never referred for CHD screening. Despite all facts we still believe that we were able to highlight the current spectrum of CHD in such children.

CONCLUSION

This is the first study of Pakistan where a large number of Down syndrome patients with CHD

have been studied for the spectrum of CHD. Out of the referred children with DS for CHD screening 77.6% have CHD with a significant high number of cases of Acyanotic CHD. VSD is the most common acyanotic CHD while TOF is the most common cyanotic CHD.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Abdul Razzaq Mughal	Principal investigator and wrote the article.	
2	Zaigham Rasool Khalid	Refered patient for evaluation from surgery different, Helped in analysis of data.	
3	Bismah Safdar	Evaluated the Pts of down syndrome, Helped in wroting introduction of the article.	
4	Safia Mughal	References down syndrome patients often bislt for CHD evaluation, helped in writing discussion.	