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Original Article

A study to determine the prevalence of pulmonary arterial hypertension in children with Down syndrome and congenital heart disease

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ABSTRACT

Background: Down syndrome (DS) is a common chromosomal abnormality associated with congenital heart disease (CHD). These cardiac abnormalities are known to be associated with pulmonary arterial hypertension (PAH).

Methods: The aim of this study was to assess the prevalence of PAH in DS children with CHD and to compare it with PAH prevalence in non-syndromic children with CHD. It was a cross-sectional study including all children presenting to Cardiology Department at a tertiary care center between Jan 2007 and Dec 2010.

Results: Thirty-five DS children with CHD were compared with 38 non-syndromic children with CHD. Atrioventricular septal defect (AVSD, 13/35) was the commonest CHD among DS children while isolated VSD (26/38) accounted for maximum cases in non-syndromic CHD. PAH was more prevalent among DS children with CHD (18/42) than among the control group (7/38, $p = 0.038$). In addition, 14/19 patients with AVSD in the entire cohort developed PAH.

Conclusion: DS children with CHD have a higher predisposition to develop PAH, and the likelihood is highest with underlying AVSD.

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Introduction

Down syndrome (DS) is a well-recognized genetic condition associated with several medical morbidities, especially congenital heart disease (CHD). CHD has been suggested to

be present in 50% of children with DS.¹ A study by the Atlanta Down Syndrome Project identified 227 patients with DS and characterized the CHD defects, revealing atrioventricular septal defects (AVSD) to be the most common abnormality.²

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It is well recognized that one of the complication of CHD in patients with DS is the development of pulmonary arterial hypertension (PAH).³ PAH is the development of raised pulmonary arterial (PA) pressure, and is defined as a mean PA pressure of >25 mmHg at rest with no evidence of left atrial hypertension (with a pulmonary capillary wedge pressure <15 mmHg).⁴ In addition, it has been suggested that the children with Down syndrome with large left-to-right shunt lesions tend to develop PAH much earlier than normal children with similar defects.^{5,6} Children with Down syndrome and atrioventricular septal defect (AVSD) or large ventricular septal defect (VSD) are often referred for surgery earlier than a non-Down syndrome child with the same heart defect.^{6,7} The data from the developed nations have illustrated a higher likelihood of development of PAH among the patients with DS and CHD, than the patients who have CHD without any syndromic association. Nonetheless, there is a paucity of data from our country about the incidence and prevalence of PAH in patients with DS and CHD. This can have significant diagnostic and therapeutic implications while managing the patients of DS.

Hence, the research question was raised to study the pulmonary artery pressure in Down syndrome children with CHD, and to compare the pressures, with a control group of non-syndromic children with CHD.

Materials and methods

Patients

A prospective observational study was performed at a tertiary care center in India from Jan 2007 to Dec 2010. All children ≤ 12 years of age, with DS and CHD, were included as the study group. The children with ventricular septal defects were included only if they had a large defect i.e., the diameter of the defect is approximately equal to the diameter of aortic annulus.⁸ The details regarding the medical history, physical examination and karyotype were recorded. Non-syndromic children were taken as control and similar data was recorded for them. The patients were excluded if they had undergone any previous corrective surgery for CHD, or if they had other systemic illnesses (sickle cell disease, connective tissue disorder, chronic lung disease, persistent pulmonary hypertension of newborn) that could influence pulmonary pressures. In addition, the patients were excluded if they were receiving sildenafil or bosentan. However, they were included in the study if they were receiving other medications including angiotensin- converting- enzyme inhibitors, diuretics, or digoxin.

Methodology

The diagnosis of DS was established based on demonstration of chromosomal abnormality on peripheral blood cell karyotype among the patients with phenotypic features suggestive of DS. The children with congenital heart diseases were classified as non-syndromic if there was no clinical dysmorphism and there were no phenotypic features suggestive of any syndrome. These children comprised the control group.

The control group, with no obvious dysmorphism was not subjected to karyotype analysis. The entire cohort of patients (study group of DS and control group of non-syndromic children with CHD) were subjected to 2 dimensional echocardiography (2D-Echo), M-mode echo, continuous wave Doppler and color flow imaging. The diagnosis of PAH was established by demonstrating PA pressure >25 mmHg at rest. Cardiac catheterization was performed only if echocardiography was inconclusive.

Statistical analysis

Summary statistics, including means, medians, and proportions were used to describe patients' baseline characteristics. Binary group comparisons were made using χ^2 or Fischer exact test as appropriate. Statistical analysis was done using GraphPad Prism version 5.00 for MacOSX (GraphPad Software, San Diego California USA).

Results

Demographic data

Seventy-three children participated in the study, 38 in the control group and 35 children with DS and CHD constituted the study group. The baseline characteristics and distribution of congenital heart diseases in the two groups has been depicted in Table 1. Cardiac catheterization was required for only one patient with DS; for all the remaining patients the diagnosis was made on 2D-Echo. The mothers of all children participating in the study were seronegative for human immunodeficiency virus.

Pulmonary artery pressure evaluation

The PA pressures were higher among the patients with DS than among the control group ($p < 0.05$, Table 1). Among patients with DS and CHD, the mean PA systolic pressure was 51 (14.2–79.8) mmHg. The corresponding mean PA systolic pressures among the control group were 26 (12–58) mmHg.

Overall pulmonary artery hypertension (PAH) was observed in 18/35 (51.4%) patients of the study group and 7/38 (18.4%) patients of control group ($p = 0.038$, Table 1). Of 18 children of PAH in study group, 10/18 (55.56%) cases were of AVSD, 7/18 (38.89%) of VSD, and 1/18 (5.56%) of ASD with PDA. The underlying CHD for the seven children with PAH in the control group included, AVSD (4/7, 57.14%), and VSD (3/7, 42.86%).

PAH and type of CHD

Among the study group 10/13 (76.92%) patients with AVSD developed PAH. This was comparable to the control group where 7/11 (63.63%) patients with AVSD developed PAH ($p = 0.35$). The prevalence of PAH among the patients with isolated VSD and DS was 7/11 (63.63%), and was statistically greater than the prevalence of PAH among non-syndromic patients with isolated VSD (3/26[11.53%], $p = 0.02$, Table 2).

Table 1 – Patient characteristics at the baseline are depicted along with the comparison of congenital heart diseases (CHD), pulmonary artery pressures, and the prevalence of pulmonary artery hypertension (PAH) between the study and control group.

Variable	Study group N = 35	Control group N = 38	p
Age (months)	17.46 ± 13.66	20.21 ± 17.24	<0.05
Mean ± SD			
Gender			
Male	20	19	>0.05
Female	15	19	
Age distribution			
0–6 m	13	12	
7–12 m	14	11	
1–4 y	5	9	
>4 y	3	6	
Types of CHD, n (%)			
AVSD	13 (37.1%)	6 (15.8%)	0.06
Isolated VSD	11 (31.4%)	26 (68.4%)	<0.05
Isolated ASD	4 (11.4%)	3 (7.9%)	0.7
Isolated PDA	2 (5.7%)	2 (5.3%)	1
ASD + PDA	3 (8.6%)	0 (0%)	0.11
VSD + PDA	1 (2.9%)	0 (0%)	0.48
ASD + VSD	1 (2.9%)	1 (2.6%)	1
Pulmonary artery systolic pressure (mmHg), Mean (range)	51 (14–79)	26 (12–58)	0.04
Prevalence of PAH, n (%)	18 (51.4%)	7 (18.4%)	0.04

The pulmonary pressures recorded across different CHD were comparable between the DS and non-syndromic group. The PA pressures have been illustrated in Table 3.

PAH and age

The PA pressures were compared across different age groups between DS and non-syndromic children for AVSD and isolated VSD heart defects. The PA pressures were comparable between the 2 groups in both AVSD and isolated VSD ($p > 0.05$, Table 3).

Discussion

Down syndrome is the most common of chromosomal disorder and the most commonly identified syndrome with heart defects.⁶ We demonstrate AVSD to be the commonest CHD among children with DS. The prevalence of AVSD among children with DS was 13/42 (30.95%) as compared to 6/38 (15.8%) in the control population. Among the control group the commonest CHD was isolated VSD accounting for 26/38 (68.4%) cases. This is in congruence with the reported literature wherein AVSD has been reported to be the commonest

CHD in DS and accounts for only 2.9% cases in the general population.^{2,9,10}

The prevalence of PAH was statistically greater among children with DS and CHD (18/35, 51.4%) than among patients with non-syndromic CHD (7/38, 18.4%, $p = 0.038$). In addition, the mean PA pressures were statistically higher among the patients with DS ($p = 0.04$). This is consistent with the findings of an earlier study, where Vazquez-Antona et al comparing 16 patients of DS with different types of CHD and 14 patients with CHD without chromosomal pathologies demonstrated that DS with CHD had greater predisposition to develop irreversible PAH especially with AVSD.¹¹ There are several known causes of PAH among children. Of particular relevance to patients with DS are left-to-right shunt and upper airway obstruction.³ Upper airway obstruction may result from obstructive sleep apnea, a condition well recognized to be associated with DS.¹² It has been estimated that obstructive sleep apnea affects just 3% of the general population compared with 30–50% of patients with DS.¹² In addition, there is some evidence that infants with DS have a degree of pulmonary hypoplasia. Although not well documented, the original work by Cooney looked at the lung architecture in just seven children and found poor development of respiratory architecture in six cases, although this was a selected and a small group of patients.¹³ However, there is evidence that the incidence of PPHN is higher in DS at 5.2% than in neonates without DS and this may relate to the possible presence of pulmonary hypoplasia.¹⁰ Fukushima et al have suggested that the predominant biosynthesis of TXA₂ over PGI₂, leading to vasoconstriction, was observed in DS infants, irrespective of the presence or absence of PAH. This imbalance in the biosynthesis of vasoactive eicosanoids may account for the rapid progression of pulmonary vascular obstructive disease in DS infants with a left-to-right shunt.¹⁴

Table 2 – Pulmonary artery hypertension across different congenital heart diseases.

	Total no.	Pulmonary artery hypertension, N (%)	p
AVSD			
Study	13	10 (76.92%)	0.35
Control	6	4 (66.67%)	
VSD			
Study	11	7 (63.63%)	0.02
Control	26	3 (11.53%)	

Table 3 – Pulmonary artery systolic pressure in AVSD and VSD in different age groups.

		Pulmonary artery systolic pressure (mm of Hg)							p
		No	Minimum	Maximum	Mean	SD	Median	SE of mean	
AVSD									
0–6 months	Study	8	64.66	84.64	70.48	2.41	68.64	1.39	0.74
	Control	3	30.61	58.15	38.60	16.31	33.24	5.78	
7–12 months	Study	5	46.34	79.61	53.73	10.01	54.40	5.79	0.89
	Control	3	33.04	50.46	32.02	18.76	34.27	6.65	
VSD									
0–6 months	Study	4	17.24	48.04	31.89	15.31	31.14	3.16	0.98
	Control	5	24.12	44.45	31.86	15.43	24.12	3.08	
7–12 months	Study	4	23.12	58.49	34.38	17.19	29.22	3.43	0.54
	Control	10	23.98	32.64	29.49	11.76	30.68	2.37	
1–4 years	Study	3	46.08	67.22	59.91	23.95	48.44	4.79	0.73
	Control	9	20.14	52.43	39.71	19.85	34.67	3.97	
> 4 years	Study	0	—	—	—	—	—	—	0.08
	Control	2	64.89	55.56	35.22	37.11	65.22	3.41	

Clapp et al¹⁵ and Suzuki et al¹⁶ reported that DS patients with complete AVSD had greater degree of elevation of pulmonary vascular resistance in the first year of life and more rapid progression to fixed pulmonary obstructive disease than children with normal karyotype. Also, Figueroa et al¹⁷ showed that 50% of patients of DS with CHD had PAH and this was especially more prevalent in patients with AVSD (89% of cases). We illustrate that 10/13 (76.92%) patients with DS and AVSD developed PAH compared to 4/6 (66.67%, $p = 0.35$) patients of AVSD in the control group. Due to a small sample size and smaller number of patients with AVSD in the control group, the difference between the groups is not significant and may not be definitive. Also, the mean PA systolic pressure recorded in our study was 51 (14–79) mm of Hg in DS with CHD while in the control group the mean PA systolic pressure was 26 (12–58) mm of Hg ($p < 0.05$). Overall, 14/19 (73.68%) cases with AVSD developed PAH within 1 year of life and this was in agreement with literature.^{15,16} Furthermore, our data corroborates with the literature that ~50% of patients of Down syndrome with CHD have PAH and AVSD is the defect most predisposed to develop PAH.¹⁶

There were several limitations in our study. Firstly, our work is limited by a small sample size and may not be representative of general population. DS though the commonest chromosomal aberration, may not have substantial representation in cardiology center, and patient accrual may be less. Secondly, we used only 2D-Echo to make the final diagnosis. Though well standardized, 2D-Echo can have intra- and inter-observer variability and cardiac catheterization continues to be the gold standard. We performed cardiac catheterization in cases with unequivocal 2D-Echo. In addition, this was a single center study spanning over three years. This can result in selection bias. Despite these short comings, we demonstrate that PAH is commoner among children with DS and CHD than in the children with non-syndromic CHD, and the likelihood of developing PAH is the highest with AVSD than with other cardiac defects.

To conclude, nearly 5 out of 10 children with Down syndrome and CHD are likely to develop PAH. This likelihood increases to almost 8 out of 10 Down syndrome children with AVSD. Though our findings need to be substantiated by larger

trials, but awaiting those studies, it is suggested to initiate timely screening of these children for PAH at an earlier age for expedient institution of PAH therapy.

Conflicts of interest

All authors have none to declare.

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