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Original Research Article

Prevalence of pulmonary arterial hypertension in children with down syndrome attending new 500 bedded paediatric hospital, Government Medical College, Srinagar

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ABSTRACT

Background: Children with Down syndrome are at increasing risk of developing pulmonary hypertension (PH) due to multiple factors. The high frequency of PH in this population has probable genetic, congenital, and environmental contributions.
Methods: This prospective observation study was conducted in the Post Graduate Department of Pediatrics, New Pediatric Hospital GMC Srinagar, on all Indoor/Outdoor patients with karyotype documented cases of Down syndrome over a period of 2 years between December 2020 to December2022. After detailed history and examination routine baseline investigations both screening and diagnostic echocardiography was done. CT was done in selected patients. In some patients, whose history and examination was suggestive of obstructive sleep apnoea (OSA), polysomnography and OSA questionnaire was used to make the diagnosis.
Results: This study included 306 children with karyotype documented Down syndrome. Out of them 72 were identified with PAH (Echocardiography documented) and the prevalence was 23.5%. Out of these 72 patients, 41(57%) were males and 31(43%) were females with male: female ratio of 1.3:1 and maximum no. of patients were present in age group 1-6months. Out of them 60 (83%) patients had underlying echocardiographic documented CHD, 10 (14%) patients had OSA (Obstructive Sleep Apnea) and 2 (3%) had GERD (Gastrointestinal Reflux Disease).
Conclusions: The PH is common in children with Down syndrome, is typically transient related to CHD or PPHN but can recur in setting of respiratory disease such as obstructive sleep apnea, intermittent hypoxia and recurrent pneumonia.

Keywords: Pulmonary arterial hypertension, Down syndrome, Congenital heart disease, Echocardiography, Obstructive sleep apnea

INTRODUCTION

Down syndrome (Trisomy 21) is the most common chromosomal disorder named after DR. John Langhan Down who first described it in 1866.[1] The incidence reported being 1:800 to 1:1000.[2] Children with Down syndrome are at increasing risk of developing pulmonary hypertension (PH) due to multiple factors as follows:[3] congenital heart disease with persistent left-to-right shunts;[4] chronic upper airway obstruction;[5] abnormal pulmonary vasculature growth;[3-6] alveolar hypoventilation;[5,7,8] pulmonary tissue damage;[9] recurrent pulmonary infections;[9] a thinner media of the pulmonary arterioles;[9,10] a diminished number of alveoli which aggravate pulmonary vascular disease (PVD).[3,4,6,9,10] DS is the most common genetic syndrome associated with PH and the others being DiGeorge syndrome, Schimitar syndrome, Noonan syndrome, Durun and Cantu Syndrome.[11] The high frequency of PH in this population has probable genetic, congenital, and environmental

contributions.[12] While the lifetime prevalence remains unknown, reports of PH incidence in childhood may be as high as 28% in this population.13 The etiology of PH in persons with DS varies; however, there is a strong association with congenital heart disease (CHD), which is present in 38–58% of this population[14-17]. Those without CHD also appear to be at higher risk of developing PH when compared to the general population, and there are likely additional respiratory and cardiovascular reasons for this increase. The World Symposium on Pulmonary Hypertension (WSPH) classifies PH into five major groups, including pulmonary arterial hypertension (PAH; Group 1); PH due to left-sided heart disease (Group 2); PH due to lung disease or hypoxia (Group 3); chronic thromboembolic PH (Group 4) and PH due to multifactorial, mixed or unclear mechanisms (Group 5).[18,19] Pulmonary hypertension (PH) in Down Syndrome by American Heart Association (AHA) is defined as: (1) PH: mPAP≥25 mm Hg in children >3 mo of age at sea level. (2) PAH: mPAP≥25 mmhg. (3) PAH: mPAP≥25 mm Hg, PAWP<15 mm Hg and PVRI>3 WU × M^2. (4) IPAH or isolated PAH: PAH with no underlying disease known to be associated with PAH referred to as HPAH with positive family or genetic evaluation. (5) PHVD Pulmonary Hypertensive Vascular Disease: Broad category that includes forms of PAH but includes subjects with elevated TPG (mPAP−left atrial pressure or PAWP >6 mm Hg) or high PVRI as observed in patients with cavopulmonary anastomoses without high mPAP.

The etiology of pulmonary hypertension in individuals with Down syndrome is not always straightforward and can often be attributed to multiple underlying challenges to the pulmonary vascular system, including increases in hemodynamic stress, abnormalities in lung development, intrinsic endothelial dysfunction, increases in pulmonary vascular resistance, and post-capillary disease As such, a better understanding of the etiology of PH in the population with DS is necessary to help determine appropriate screening and interventions. The aim of our study was to identify prevalence and risk factors for PAH in children with Down syndrome.

METHODS

This prospective observation study was conducted in the Post Graduate Department of Pediatrics, New Pediatric Hospital GMC Srinagar, on all indoor/outdoor patients with karyotype documented cases of Down syndrome over a period of 2 years from December 2020 to December 2022. Our study was approved by the ethical committee of Government Medical College Srinagar via communication no. (Minutes-BOPGS) Acad/KU/22 02-02-2022 held on 29th and 30th September 2021 under serial number 13 and written informed consent was obtained from parents or guardians of the children included in the study. In this study 306 children with karyotype documented Down syndrome were evaluated for PAH. After detailed history and examination routine baseline investigations including (CBC, LFT, KFT, ABG, Chest X-ray, ECG) was done. Screening and diagnostic echocardiography was performed.

PAH was defined on the basis of echocardiographic criteria (Right heart catheterization could not be done since it was a noninvasive study) as mPAP≥25 mmhg which is identified by 1, TR peak velocity (a value of >3.4 m/s suggestive of PAH.) 2, Peak PR Doppler and 3, RAP (mPAP =4(PR velocity)2 + RAP). CT was done in selected patients. In some patients, whose history and examination was suggestive of obstructive sleep apnoea (OSA), polysomnography and OSA questionnaire was used to make the diagnosis.

Inclusion criteria

All children (1 month to 18 years) with karyotype documented Down syndrome were included in the study.

Exclusion criteria

All infants of age less than 1 month were excluded from the study.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel0 and then exported to data editor of statistical package for social sciences version 20.0 (SPSS Inc., Chicago. Illinois, USA). Continuous variables were expressed as Mean and categorical variables were expressed as frequencies and percentages.

RESULTS

In our study a total of 306 patients with Down syndrome (Karyotype Documented) were examined during the study period. Out of them, 72 were identified with PAH (Echocardiography Documented) and were included in this study. So the prevalence of PAH was 23.5%. Out of these 72 patients, 41 (57%) were males and 31 (43%) were females with male: female ratio of 1.3:1. Out of 72 children, the maximum number of patients, 22 (30%), were in the age group of 01-06 months, followed by 16 (22%) in the age group of 01-03 years followed by 15 (21%) in the age group of 6 months to 1 year, and 10 (14%) in the age group of 3 to 6 years and the least number, 9 (13%) in the age group of 06-18 years as depicted in Table 1. Maximum patients were in the age group of 1 to 6 months. In this study, maximum patients were presented with dyspnea 24 (33%) followed by cough (17%), fever (12%), failure to thrive (11%), cyanosis 4 (6%), irritability 3 (5%), syncope 4 (6%), dizziness 3 (4%), palpitation 3 (4%), chest pain 4 (5%).

In this study, baseline biochemical and radiological investigations were done and shown in Table 2. Echocardiography was done in all patients. Among them 60 patients had left to right shunt with severe PAH, which include, complete AVSD (25), large VSD (11),

large PDA (8), single ventricle with PAH (9) and multiple defects (7). 12 patients had structurally normal heart. They were grouped into mild (7), moderate (3) and severe PAH (2), with following echo findings, TR jet velocity of >3.4 m/s was identified in 5 patients, RV/LV ratio of >1 was identified in 4 patients, peak PR Doppler signal in 3 patients. ECG was done in all patients, 30 patients had normal ECG findings, 15 patients had northwest deviation, 10 patients had biventricular hypertrophy, 8 patients had RVH (right ventricular hypertrophy), 5 patients had T wave strain, 4 patients had P pulmonale. Among radiological investigations, chest X-ray was done in all 72 patients. 32 patients had underlying consolidation, suggestive of pneumonia. Cardiomegaly was present in 14 patients; 12 patients had underlying pleural effusion. 6 patients had enlarged pulmonary artery and 5 patients had prominent pulmonary conus. Among 72 patients, 3 patients were severely symptomatic, despite adequately treated for Pneumonia, CT angiography was performed, revealing enlarged pulmonary trunk and other features of PAH. In 2 patients, due to poor echocardiographic window, PAH could not be assessed and CT angiography was done revealing MPA/AA (Main Pulmonary Artery/Ascending Aorta) ratio of >1.1. We had 10 patients in the age group of 6 years to 18 years with associated symptoms of snoring and day time somnolence and BMI>30, PSQ (Pediatric Sleep Questioner with a score of >0.33) was used to evaluate them for OSA (Obstructive Sleep Apnea). Among them polysomnography (PSG) was done in 2 patients to confirm the diagnosis of OSA. 2 patients in the age group of 7-15 years had associated symptoms of gastroesophageal reflux including regurgitation, dyspepsia with structurally normal heart. In these patients, Upper Gastrointestinal endoscopy was done.

In our study 60 (83%) patients had underlying echocardiographic documented CHD. 10 (14%) patients had OSA (Obstructive Sleep Apnea) and GERD (Gastrointestinal Reflux Disease) was found in 2 (3%) patients as depicted in Table 3.

Table 1: Gender and age distribution of DS patients with PAH.

Characteristic		Frequency (N)	Percentage (%)
Gender	Male	41	57
	Female	31	43
Age (years)	Total	72	100
	1-6 months	22	30
	6 months-1 year	15	21
	1-3 years	16	22
	3-6 years	10	14
	6-18 years	9	13
	Total	72	100

Table 2: Various investigations along with their frequencies done in Down syndrome patients with PAH.

Investigation	Frequency (N)
Chest X-ray	72
Consolidation	35
Cardiomegaly	14
Pleural effusion	12
Enlarged pulmonary artery	6
Enlarged pulmonary conus	5
Echocardiograph	72
Left to right shunt with severe PAH	60
Complete AVSD	25
Large inlet VSD	11
Large PDA	8
Single ventricle with PAH	9
Multiple defects	7
Structurally normal heart	12
MILD PAH	7
Moderate PAH	3
Severe PAH	2
TR jet velocity>3.4 m/s	5
RV/LV ratio>1	4
Peak PR Doppler signal	3

Continued.

Investigation	Frequency (N)
ECG	72
Normal	30
Northwest deviation	15
Biventricular hypertrophy	10
RVH	8
T wave strain	5
P pulmonale	4
CT angiography	7
Enlarged pulmonary trunk	3
MPA/AA ratio> 1.1	2
Bilateral consolidation	2
Pediatric sleep questionaire	10
Polysomnography (PSG)	2
UGI endoscopy	2

Table 3: Various etiologies of PAH in patients with Down syndrome.

Etiology	Frequency (N)	Percentage (%)
CHD (left to right shunt with severe PAH)	60	83
Complete AVSD	25	35
Large inlet VSD	11	15
Large PDA	8	11
Single ventricle with PAH	9	12
Multiple defects	7	10
Structurally normal heart with PAH	12	17
OSA	10	14
GERD	2	3
Total	72	100

DISCUSSION

Pulmonary hypertension is frequently identified in individuals with Down syndrome. The etiology of PH in persons with DS varies; however, there is a strong association with congenital heart disease, which is present in 38–58% of this population. Those without CHD also appear to be at higher risk of developing PAH when compared to the general population, and there are likely additional respiratory and cardiovascular reasons for this increase. 306 patients of karyotype documented Down syndrome were examined during the study period. Out of them, 72 patients were found to have echocardiography documented PAH and were included in this study. In this study, the prevalence of PAH is 23.5%. The recent meta-analysis by Taksande et al[18] identified that the pooled prevalence of PH in Down syndrome was 25.5%. In the study of Alhuzaimi et al, the prevalence of PH was 23.7%.[20] In the study of Shrestha et al, the prevalence of PH was 52.5%.[21] This may be low as the neonates with the prevalence of PPHN were excluded in this study and because of genetic and environmental factors. In the present study (57%) were males, and (43%) were females, with a male female ratio of (1.3:1). In the study of Banjar HH22, the male-female ratio was (1.3:1) and in the study of Espinola-Zavaleta et al, male-female ratio was (1:1).[13] In this study, a maximum number of children were in the age group of 1 to 6 months followed by 1 to 3 years. In the study of Weijerman et al, the mean age was 3 months.[23] In the study of Alhuzaimi et al, more the half of the study population was below 6 months.[20] This is explained as the screening for congenital heart defects is usually done in early infancy. In this study, maximum patients were presented with dyspnea 24 (34%), followed by cough 12 (20%), fever 9 (13%), failure to thrive 8 (11%), cyanosis 8 (11%), irritability 3 (5%), syncope 4 (5%), dizziness 3 (4%), palpitation 3 (4%), chest pain 2 (2%). In the study of Berger et al, similar clinical profile was identified with maximum patients presented with dyspnea (65%) followed by fatigue (41%) and followed by syncope (20%).[24] In the study of Kwiatkowska et al, the most common symptoms identified were fatigue and dyspnoea.[25]

In this study 60 patients had left to right shunt with severe PAH, which include, complete AVSD (25), large VSD (11), large PDA (8), single ventricle with PAH (9) and multiple defects (7). 12 patients had structurally normal heart. They were further grouped into mild, moderate and severe PAH based on following echocardiographic findings. (1) TR jet velocity of >3.4 m/s (2) RV/LV ratio of >1 (3) peak PR Doppler. ECG was done in all patients. 30 patients had normal ECG findings, 15 patients had northwest deviation, 10 patients had biventricular hypertrophy, 8 patients had RVH (Right

Ventricular Hypertrophy), 5 patients had T wave strain and 4 patients had P pulmonale. Among radiological investigations, chest X-ray was done in all 72 patients. 32 patients had underlying consolidation, suggestive of pneumonia. cardiomegaly was present in 14 patients; 12 patients had underlying pleural effusion. 6 patients had enlarged pulmonary artery and 5 patients had prominent pulmonary conus. Among 72 patients, 3 patients were symptomatic, despite adequately treated for Pneumonia (radiologically confirmed), CT angiography was performed which revealed enlarged pulmonary trunk and other features of PAH. In 2 patients, due to poor echocardiographic window, PAH could not be assessed and CT angiography was done which revealed MPA/AA (Main Pulmonary Artery/Ascending Aorta) ratio of >1.1. We had 6 patients in the age group of 6 years to 18 years with associated symptoms of snoring and day time somnolence and BMI>30, PSQ (Pediatric Sleep Questioner with a score of >0.33) was used to evaluate them for OSA (Obstructive Sleep Apnea). Among them polysomnography was done in 2 patients to confirm the diagnosis of OSA. 2 patients in the age group of 7-15 years had associated symptoms of gastroesophageal reflux including regurgitation, dyspepsia with structurally normal heart. In these patients' Upper Gastrointestinal endoscopy was done. In the present study 60 (83%) patients had underlying echocardiographic documented CHD (Left to right shunt with severe PAH). 10 (14%) patients had OSA (Obstructive Sleep Apnea). GERD was found in 2 (3%) patients. In the study of Housten et al, 82% of DS with PAH had associated CHD most common include AV canal defects.[24] In the study of Espinola-Zavaleta et al, CHD was associated in 80% of patients with PAH.[13] In this study, 60 (83%) patients had CHD (Left to right shunt with severe PAH). The most common CHD's were complete AVSD (35%), large inlet VSD (15%), multiple defects (10%), large PDA (11%), single ventricle with PAH (12%). In the study of Housten et al, 82% of DS with PAH had associated CHD, most common include AV canal defects.[24] In the study of Alhuzaimi et al, the prevalence of pulmonary hypertension was noted to be highest among patients with AVSD (34.4%), followed by hemodynamically significant PDA (36.4%), followed by ASD secundum (22.9%), then VSD (12.2%).[20] In this study, 10 (14%) patients with PAH with structurally normal heart had underlying OSA. In the study of Banjar, 34% of the patients with Down syndrome were found to have PAH associated with OSA.[10] In the study of Maloney et al, 8.2% of the patients with OSA were found to have PAH.[24]

Limitations

The main limitation of our study was that not all the studies had classified all the etiologies of PH as per the WHO classification. The paucity of etiological data made it difficult to delineate individual causes of PH in patients with DS and this added to existing heterogeneity while analyzing the exact prevalence of PAH in DS. More studies, specifically, ones with the community screening in our valley for PH in DS are required to come to an exact estimate.

CONCLUSION

PAH appears to be more common in population with DS than that in the population without DS. This is accounted for by the high prevalence of underlying CHD's in these children. In order to improve the care given and to reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his or her efforts towards routine screening of PAH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS in the absence of CHD's.

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