Is Down Syndrome Related to Pulmonary Arterial Hypertension? A Comparative Study

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Abstract- Down syndrome (DS) is a genetic impairment associated with comorbidities such as Congenital Heart Disease (CHD). Pulmonary Arterial Hypertension (PAH) is a complication of CHD in most patients. Due to insufficient documents about the prevalence of PAH in DS with CHDs compared to non-DS (NDS)+CHD patients, this study aimed to compare the prevalence of PAH between DS-CHD and NDS-CHD patients. This is a cross-sectional study conducted on DS-CHD patients referred to the Pediatric and Congenital Cardiology Division at Imam Reza training hospital in Mashhad, Iran, between April 2015 and February 2016. The comparison group included NDS-CHD children matched in terms of age and gender. A comprehensive Echocardiography was run for all patients to determine the types of CHD and pulmonary arterial pressure. Seventy-seven patients were enrolled in the study (47 in the DS-CHD group and 30 in the NDS-CHD group). 48.9% of the DS-CHD patients and 23.3% of the NDS-CHD group developed PAH, which revealed a significantly higher rate of PH among DS-CHD patients (*P*=0.025). Our findings denote a higher prevalence of PAH among DS-CHD patients compared to NDS-CHD patients. Such an observation is a meaningful warning for DS patients to take early necessary medical or corrective therapies for CHD in order to prevent complications and irreversible pulmonary vascular disease.

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Introduction

Down Syndrome (DS) is the most common genetic disorder, which occurs in 1 per 800 live births (1-3) and is associated with a high burden on medical services (4).

This genetic syndrome is associated with many disorders and anomalies. Among anomalies due to this syndrome, the most prevalent is Congenital Heart Disease (CHD) (5,6) while in 40% of cases Atrioventricular Septal Defect (AVSD), Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), and valve defects are observed (1).

One of the consequences of CHD in children with DS is the early onset of Pulmonary Arterial Hypertension (PAH) which is associated with the higher prevalence of PAH in infants with DS compared to CHD patients without DS (7-11).

PAH is defined as pulmonary arterial pressure more than 25 mmHg, provided that it does not result in left atrium pressure increasing (12). Abnormal growth of pulmonary vessels and alveolar decreased number (reduction in alveolar radius) are the most important causes of PAH in children with DS. Development of PAH in children with CHD-DS is faster so that 5% of children with large VSD have progressed to PAH during the first two years of life (13,14).

An increase in pulmonary blood flow leads to shear damage in the vessels and irreversible side effects (15,16).

Based on an article from the Pune University of India,

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the prevalence of PAH in CHD-DS patients was 51.4% and in children with CHD was 18.5%. In the case group, the mean of the PAH was significantly higher than the control group (12).

Considering the insufficient evidence to compare PAH in DS-CHD and NDS-CHD in Iran and the necessity for prevention and early prediction of PAH in DS patients can lead to a decrease in mortality, morbidity rate, and their financial and social problems.

Materials and Methods

This is a cross-sectional study with nonprobability-convenient sampling. The case and comparison groups were chosen from DS-CHD and NDS-CHD children, respectively, referred to the Pediatric Cardiology Clinic of Imam Reza Hospital, Mashhad, Iran (from April 2015 to February 2016). Informed consent was taken from all participants in the study. Children with persistent pulmonary hypertension of the newborn (PPHN) and another disease with primary pulmonary hypertension were excluded. The sample size in the CHD-DS group was calculated 47 patients with reliability 95% and relative accuracy of 0.3. The 30 NDS-CHD children matched in age and gender were selected as the comparison group. Echocardiography (Samsung HS70) was done for all patients to determine CHD types and pulmonary arterial pressure. Echocardiography assessments were conducted by the specialist in congenital heart diseases in pediatrics. Measurement of pulmonary arterial pressure by echocardiography was based on the ESC Guideline (European Pulmonary Hypertension guideline) in the following way:

The pulmonary artery systolic pressure (PASP) rate in the absence of obstruction of right ventricle outlet was approximately the same as right ventricular systolic pressure, and pressure measurement at the valve level was available by using the Bernoulli method. Bernoulli's equation is:

$$PASP \rightarrow RVSP = 4 \times (VTR) \times 2 + RAP$$

The maximum of pulmonary artery pressure (PAP) is measurable in the presence of tricuspid regurgitation (TR), and the average of PAP is measurable in the presence of pulmonary insufficiency (PI). The peak velocity at the tricuspid valve level more than 2/8 m/s and PASP more than 36 mmHg in the absence of other echocardiographic findings are suggestive for PAH while flowing more than 3/4 m/s, PASP more than 50 in the presence of TR demonstrates a definite diagnosis (4).

In our study, PAH is defined as the mean of PAP more than 25 mmHg.

Finally, the echocardiographic findings and patients' information were entered into a prepared checklist. It should be noted that in terms of demographic characteristics, two groups were matched and homogenized.

Statistical analysis

Statistical analyses were performed using SPSS software version 17 for windows (IBM Inc, NY). To compare the prevalence of PAH between two groups, the Pearson Chi-square test was used. Also, for other qualitative variables, the Pearson Chi-square test and Fisher's Exact test were used. For other quantitative variables, *t*-test and Mann-Whitney test were used. For all variables level of significance is $P<0.05$.

Results

This study was conducted on 77 patients (47 DS-CHD patients and 30 NDS-CHD patients as a comparison group). Among 47 DS-CHD patients (Mean±SD age: 15.1±25.83 Months), 34% were male and 66% were female. In the comparison group (Mean±SD age: 36.6±44.17 months), of 30 subjects, 43.3% were male and 56.7% were female. Statistical analysis demonstrates that there are no significant differences in age ($P=0.108$) and gender ($P=0.412$) between the two groups. The findings related to CHD in DS and NDS patients were presented in Table 1.

Based on the findings, there were no significant differences between the two groups in types of CHD. While this difference insignificant in PAH (Table 2).

Besides, the examination of mean pulmonary arterial pressure based on the pressure calculated at the valve level of the pulmonary in those with PI showed that this amount in the DS group and control groups were 33.3±18.90 mmHg and 26.1±13.31 mmHg, respectively, which shows no statistically significant difference between two groups (Table 2).

In relation to pulmonary hypertension, the analysis indicated that 23 subjects (48.9%) of the DS group and seven subjects (23.3%) of the control group had pulmonary hypertension ($P=0.02$) (Table 2).

Table 1. Frequency and comparison of cardiac anomaly types in Down syndrome and Non-DS groups*

Anomaly Type	DS Group (N=47)	NDS Group (N=30)	*P*
AVSD	19.1% (n=9)	3.3% (n=1)	0.078*
ASDp	21.3% (n=10)	10% (n=3)	0.198*
ASDs	29.8% (n=14)	26.8% (n=8)	0.768
VSD	61.7% (n=29)	56.7% (n=17)	0.660
PDA	40.4% (n=19)	16.7% (n=5)	0.028*
CoA	0% (n=0)	13.3% (n=4)	0.020*
TOF	6.4% (n=3)	16.7% (n=5)	0.250*
PI	46.8% (n=22)	26.7% (n=8)	0.077
TR	46.8% (n=22)	46.7% (n=14)	0.990
PS	12.8% (n=6)	23.3% (n=7)	0.227
PFO	27.7% (n=13)	16.7% (n=5)	0.266

*Fisher's exact test, Pearson Chi-Square

Table 2. Measured pulmonary artery pressure

	DS Group (N=47)	NDS Group (N=30)	*P*
Maximal Pulmonary Artery Pressure Using TR (mmHg)	53.7±14.45 (n=22)	44.0±26.72 (n=14)	0.227*
Mean Pulmonary Artery Pressure Using PI (mmHg)	33.3±18.90 (n=22)	26.1±13.31 (n=8)	0.332
Frequency of Pulmonary Hypertension in two Groups	48.9% (n=23)	23.3% (n=7)	0.025

*Independent Samples t-test, Pearson Chi-Square

Discussion

The majority of patients in the DS group (63.8%) had a kind of heart complex abnormalities. The most common abnormalities were VSD, ASD, and PDA, respectively. The prevalence of PAH in DS patients was 48.9% which was significantly higher than the comparison group (23.3%).

In different studies, the high prevalence rate of AVSD, ASD, VSD, and PDA in DS patients has been reported. Although the prevalence rate was different in the majority of them, AVSD was the most common abnormalities in patients (17).

In this study, with attention to the referral research center and this point that all individuals have CHD, the results were slightly different; Beside the majority of patients were outpatients and their clinical conditions were better. Therefore, the probability of underestimation of serious abnormalities like AVSD is higher than in other studies. Due to the small sample size of our study (which was determined based on the main purpose of the study), our sub-results cannot perfectly show the actual conditions of DS patients in Iran.

Based on the echocardiographic criteria for PAH diagnosis, the results have shown the prevalence of PAH in DS patients (49%) was significantly higher in comparison with NDS patients (23%) (Two groups have not significant difference in gender, age, and heart anomaly types).

There are no studies that compare the prevalence of PAH in DS-CHD and NDS-CHD in our country. So, the present study has novelty and emphasizes on early management of these patients before remarkable clinical manifestations.

In a study by Alsuwayfee *et al*. (18), 76 DS children (mean age: 19.9±3.7 months) and 76 NDS children (mean age: 9.5±2.03 months) were evaluated by echocardiography assessments. The findings indicated that congenital heart diseases are more prevalent significantly compared to NDS patients (most common CHDs are atrioventricular septal defect and ASD). This finding is the same as the present study. Also, 30% of DS patients have PAH, which significantly higher than NDS patients. They concluded that the high prevalence of CHDs in DS patients is associated with higher PAH (18).

Also, Espinola-Zavaleta *et al*., (19), assessed CHDs and PAH in DS patients. In this study, 127 DS patients in Mexico City were evaluated through physical exam, echocardiogram, and electrocardiogram. In terms of CHD, 40% of DS Patients were suffered from CHD. 80% of them had PAH (Mean Pulmonary Artery Pressure: 32±11 mmHg). The findings related to DS patients with and without CHD revealed more PAH in DS-CHD compared to DS patients without CHD (odds ratio: 7.3

versus 3) (19). Although the present study classified DS-CHD and NDS-CHD patients, our findings concluded a higher prevalence of PAH in DS patients.

In another study from India, the prevalence of PAH was significantly higher in the patients with DS and CHD compare with the NDS patients with CHD (51.4% vs. 18.4%, *P*=0.038) (12). Vazquez-Antona and colleagues showed CHD-DS patients have the more favorable background for present irreversible PAH, particularly with AVSD (20).

So findings of this study, like other studies in the world, have shown the higher prevalence of pulmonary arterial hypertension in DS patients with congenital heart disease. These findings remind the importance of careful management and constant follow-up in DS children because the late diagnosis of PAH reduces the effect of treatments and may lead to Eisenmenger syndrome, while corrective surgery will be contraindicated in this stage.

One of the limitations of this study was the diagnosis method based on echocardiography finding at the level of Tricuspid and Pulmonary valves in the presence of TR and PI. The definitive diagnosis of PAH is based on cardiac catheterization. In some of the patients, the echocardiographic evidence such as increasing diameter of the right heart cavity, abnormality in shape and function of the interventricular septum, increasing in right ventricle septum thickness, and the main pulmonary artery dilatation are strongly suggestive for PAH. However, the conditions for evaluation of main PAH echocardiography criteria did not exist. In this situation, catheterization and hemodynamic assessment could be very helpful.

Our results have shown the high prevalence of PAH in children with Down syndrome and CHD in comparison with NDS-CHD patients and the importance of more attention to these patients for early prediction and prevention from irreversible conditions.

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