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RESEARCH ARTICLE

CLINICAL PROFILE AND OUTCOME OF PAEDIATRIC PULMONARY ARTERY HYPERTENSION PATIENTS

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ABSTRACT

I**ntroduction:** Patterns, prevalence & outcome of Paediatric PAH have not been characterized in our local population. **Aims & Objectives**: To study the clinico-echocardiographic profile and outcome of children diagnosed as pulmonary arterial hypertension (PAH). **Material & methods:** The study was a prospective non-randomized study conducted .The study group included all the children in the age group of 0-15 years who were diagnosed as pulmonary arterial hypertension on Transthoracic Doppler Echocardiography. Detailed history, examination besides other investigations including Chest X ray, complete blood counts, ABG analysis, ECG, screening for connective tissue disorders and HIV, PBF, LFT, KFT were done as per standard guidelines. All patients were followed for one year **Results.** The total number of admissions during the study period were 22150.Total number of PAH cases were 40. PAH case represented 0.18% of the total admissions. Mean age at the time of diagnosis was 7.3 months, 23 (57.5%) of the PAH patients were females whereas 17 (42.5%) were males. The most common clinical features were irritability (82.5%), tachypnea (75%), cyanosis (70%) followed by poor feeding (65%), features of right heart failure (35%) and syncope (5%). Idiopathic PAH constituted 42.5% of the study group, whereas 50% of the PAH cases were associated with CHD. 7.5% cases were diagnosed as PPHN. The mean systolic Pulmonary Artery Pressure in the study group was 63.17 mmHg. Most of the cases had severe PAH (65%), whereas moderate and mild PAH cases were 25% and 10% respectively. PPHN Out of the total of 40 cases studied 10 patients died representing 25% mortality over 1 year. 5 had IPAH, 4 had PAH with CHD and 1 had PPHN. Mortality for different types of PAH was as follows: IPAH: 5 out of 17 (29.41%) PAH associated with CHD: 4 out of 20 (20%) PPHN: 1 out of 3 (33%) .Overall 1 year survival rate for PAH was 75%. For different types of PAH the survival rates were as follows: IPAH: 70.59% PAH associated with CHD: 80% PPHN: 66.7%. Right heart failure (p value .0001) and evidence of right ventricular systolic dysfunction (p value .04) were found significantly associated with Increased mortality **Conclusion:** In view of relatively higher incidence of idiopathic PAH observed in this study in children of Kashmir, further studies are needed to identify the role of possible genetic and familial factors. Paediatric PAH is associated with high mortality in our population. Those having Right heart failure and Right Ventricular Dysfunction need close follow up.

Key words: Paediatric PAH, Idiopathic PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a group of diseases characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death (Simonneau). When measured directly in the cardiac catheterization laboratory, the normal pulmonary artery systolic pressure of children and adults is ≤ 30 mm Hg and the mean PA pressure is ≤ 25 mmHg at sea level (Park, 2008). Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure >25mmHg at rest or >30 mmHg with exercise (Park, 2008; Hatano, 1975; Haworth, 2008; Heart 2001). The term pulmonary arterial hypertension is not synonymous to pulmonary hypertension, rather PAH is a subgroup included within the broader classification of pulmonary hypertension. Pulmonary hypertension can occur at any age although it is more common in children than adults. Pulmonary arterial hypertension is much more common than venous hypertension particularly in childhood (Haworth, 2008).

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PAH was previously considered a rare disease but the most recent evidence suggests that the prevalence of PAH is about 15 per million (Marc Humbert, 2006). In older patients females outnumber males by 1.7:1, in younger patients both genders are represented equally (Nelson Textbook of Pediatrics, 2007). Multiple etiopathogenetic pathways have been implicated in the development of PAH. The predominant cause of increased pulmonary vascular resistance causing PAH is loss of vascular luminal cross section due to excessive cell proliferation, reduced rates of apoptosis and vasoconstriction caused by decrease in nitric oxide (vasodilator) and increase in endothelin (vasoconstrictor). In less than 10% cases PAH is inherited. Most of these cases have mutation in Bone Morphogeneitc Protein Receptor type-2 (BMPR2) and rarely mutation in Activin Receptor Like Kinase type-1 (ALK-1) or Endoglin (Park, 2008; Gérald Simonneau, 2009; Vallerie, 2009 and Harrison's Principles of Internal Medicine, 2005). There is very little data from our community about the patterns and prevalence of Paedaitric PAH. In this study, an attempt has been made to identify the cases who were clinically suspected of having Pulmonary Arterial Hypertension (PAH) amongst the hospitalized

children admitted for various reas ons. All such cases underwent echocardiography and those children who fulfilled the diagnostic criteria for Idiopathic PAH (IPAH) were studied in detail to know their clinico-epidemiological profile and to have an idea on the incidence of this reportedly rare disorder in children in this part of the world.

Aims and Objectives

- To study the clinico-echocardiographic profile of children diagnosed as pulmonary arterial hypertension (PAH).
- To study the incidence of idiopathic pulmonary arterial hypertension (IPAH) in children of Kashmir Valley (Hospital based).
- To study the outcome of Paediatric PAH patients

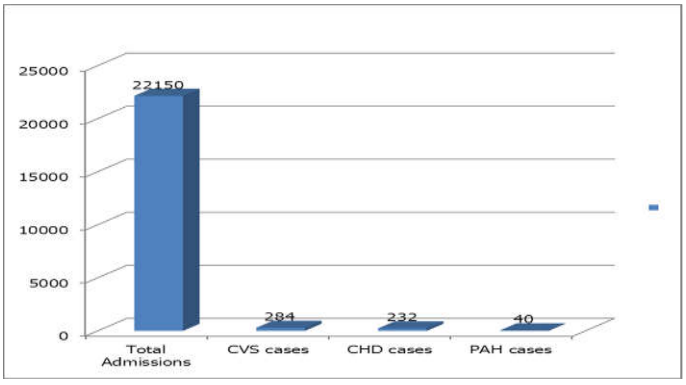
MATERIAL AND METHODS

Study Design: The study was a prospective non-randomized study conducted from September 2009 to August 2010.The study group included all the children in the age group of 0-15 years who were diagnosed as pulmonary arterial hypertension on Transthoracic Doppler Echocardiography with systolic pulmonary artery pressure (sPAP) of >35 mmHg. Only Group 1 PAH (WHO) were included in the study .The cases of PAH excluded from the study include 1. Pulmonary hypertension owing to left heart disease 2. Pulmonary hypertension owing to lung diseases and/or hypoxia 3. Chronic thromboembolic pulmonary hypertension (CTEPH) 4. Pulmonary hypertension with unclear multifactorial mechanisms.

Methods: All the cases who were clinically suspected of having pulmonary arterial hypertension amongst the hospitalized children admitted for various reasons underwent detailed relevant history and clinical examination which was recorded in the preset proforma. Chest X ray, and Other investigations included complete blood counts, ABG analysis, ECG, screening for connective tissue disorders and HIV, PBF, LFT, KFT wherever indicated. Those patients in which PAH was suspected underwent Transthoracic Doppler Echocardiography by a cardiologist having experience in pediatric cardiology using echocardiographic machine Acuson. The echocardiographically proved PAH cases were classified into mild, moderate and severe PAH on the basis of measured sPAP values. These cases were divided as: Mild PAH: 36-45 mmHg sPAP Moderate PAH: 46-55 mmHg sPAP Severe PAH: ≥ 56 mmHg sPAP The incidence of PAH and IPAH was calculated on the basis of patients presenting to the sole tertiary care hospital for children from the entire Kashmir Valley which has a children population of 2,001,340 aged 0-15 years.

OBSERVATION AND RESULTS

The total number of admissions during the study period were 22150. Total number of CVS admissions were 284. Total number of Congenital Heart Diseases diagnosed were 232. Total number of PAH cases were 40. PAH case represented 0.18% of the total admissions (Graph 1). Mean age at the time of diagnosis was 7.3 months As is evident from the Table 1 most of the PAH cases (77.5%) were in the 1 month to 1 yr age group with a highly significant p value (.006). 23 (57.5%) of the PAH patients were females whereas 17 (42.5%) were males. 75% of PAH patients were from rural area. 15 (37.5%) were 1st in birth order, 62.5% were having birth order >1. 35 (87.5%) were hospital deliveries. 16(60%) cases were delivered by normal vaginal route and 80% cases were products of non-consanguinity. The most common clinical features were irritability (82.5%), tachypnea (75%), cyanosis (70%) followed by poor feeding (65%), features of right heart failure (35%) and syncope (5%).



Graph 1. Depicting Total number of PAH cases in relation to total admissions/CHD cases

The distribution of PAH is shown in Table 2 Idiopathic PAH constituted 42.5% of the study group, whereas 50% of the PAH cases were associated with CHD. 7.5% cases were diagnosed as PPHN. However none of the patients in the study group had PAH associated with connective tissue disorder. Majority (40%) of the cases of PAH associated with CHD were having VSD(8 patients), 15%(3) cases were having either ASD or PDA or both associated with VSD. 15%(3) of cases were having Complete AV Canal Defect whereas ASD, PDA and Truncus Arteriosus comprised 10%(2) of cases each as shown in Table 3.

Table 1. Age Distribution of PAH Patients

Age	Total	p value
<1 month	4 (10%)	.08
1 month to 1 yr	31 (77.5%)	.07
1 yr to 5 yrs	5 (12.5%)	.32
6yrs to 15 yrs	0	-

Table 2. Distribution of PAH Cases, Idiopathic PAH Vs Others

	Total	Percentage
PAH with CHD	20	50
Idiopathic PAH	17	42.5
PPHN	3	7.5
PAH with CTD	-	-

Abbreviations:- CHD: Congenital Heart Disease, PPHN: Persistent Pulmonary Hypertension of Newborn, CTD: Connective Tissue Disorder

Table 3. Distribution of PAH Cases Associated with CHD

	Total	Percentage
VSD	8	40
VSD ± ASD ± PDA	3	15
ASD	2	10
Complete AV Canal Defect	3	15
Truncus Arteriosus	2	10
PDA	2	10

Abbreviations:-VSD: Ventricular Septal Defect, ASD: Atrial Septal Defect, PDA: Patent Ductus Arteriosus

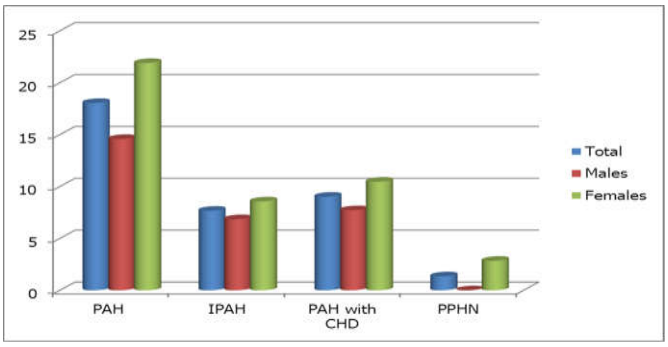
The mean systolic Pulmonary Artery Pressure in the study group was 63.17 mmHg. Most of the cases had severe PAH (65%), whereas moderate and mild PAH cases were 25% and

10% respectively. Tricuspid Regurgitation was found universally in all the cases. 95% had Right Ventricular enlargement, 80% had associated Right Atrial enlargement, systolic flattening of IVS was seen in 85%, Right Ventricular Systolic Dysfunction in 70%, Pulmonary Regurgitation in 40%, and thickened IVS in 35% (Table 4). Most of the cases had severe PAH and 85% of severe PAH cases were in the age group of 1 month to 1 year.

Table 4. Echocardiographic Profile of Patients with PAH

Echo Finding	Total number	Percentage
Mild PAH (sPAP 36-45 mmHg)	4	10
Moderate PAH (sPAP 46-55 mmHg)	10	25
Severe PAH (sPAP ≥56 mmHg)	26	65
Tricuspid Regurgitation	40	100
RV enlargement	38	95
Systolic Flattening of IVS	34	85
RA enlargement	32	80
Right Ventricular Systolic Dysfunction	28	70
Pulmonary Regurgitation	16	40
Thickened IVS	14	35

Abbreviations:- sPAP: systolic pulmonary artery pressure, IVS: interventricular septum, RV: right ventricle, RA: right atrium



Graph 2. Depicting the Total and Differential Incidence of PAH per 10000 Hospital Admissions

However this clustering of cases in the 1 month to 1 year age group is not statistically significant (p value =.81).Incidence of PAH was 18.05/10000 hospital admissions (Males 14.58/10000, Females 21.09/10000) .Incidence of Idiopathic PAH was 7.67/10000 (Males 6.86/10000, Females8.57/10000), PAH associated with CHD 9.02/10000 (Males 7.72/10000, Females 10.47/10000), and PPHN 1.35/10000 Female incidence was more than male incidence in all types of PAH(Graph 2). Out of the total of 40 cases studied 10 patients died representing 25% mortality over 1 year. 5 had IPAH, 4 had PAH with CHD and 1 had PPHN (Graph1). Mortality for different types of PAH was as follows: IPAH: 5 out of 17 (29.41%) PAH associated with CHD: 4 out of 20 (20%) PPHN: 1 out of 3 (33%). Overall 1 year survival rate for PAH was 75%. For different types of PAH the survival rates were as follows: IPAH: 70.59% PAH associated with CHD: 80% PPHN: 66.7%. The mean systolic Pulmonary Artery Pressure in the study group was 63.17 mmHg. Most of the cases had severe PAH (65%), whereas moderate and mild PAH cases were 25% and 10% respectively After analyzing the various clinico - echocardiographic risk factors associated with mortality, only two factors, features of right heart failure (p value .0001) and evidence of right ventricular systolic dysfunction (p value .04) were found to be statistically significant. Total of 14 patients had clinical features of RV failure, among them 9 patients died (64.2%) (p=0.0001). Among echocardiographic variables 28 patients had RV dysfunction, out of which 10(35.71%) (p=0.04).

DISCUSSION

The study was conducted over a period of one year. Total admissions during this period were 22150. The study was done over 40 children in the age group of 0-15 years who fulfilled the criteria for pulmonary arterial hypertension (PAH). The purpose of this study was to identify the cases who were clinically suspected of having pulmonary arterial hypertension amongst the hospitalized children admitted for various reasons, to study their clinico-echocardiographic profile, and to calculate the incidence of idiopathic PAH. Most of the studies on PAH have been done in the adult population. There is limited data available on the epidemiology of PAH in children. In our study out of 40 cases, 4 (10%) were <1 month of age, 31 (77.5%) were in the age group of 1month to 1year, 5 (12.5%) were 1year to 5 years in age and none of the patients were more than 5years of age. Majority of the cases were in the age group of 1 month to 1 year. The mean age at the time of diagnosis was 7.3 months. Rosa Laura E van Loon *et al.*[11] identified 3265 children 0-17 years of age over a period of 15 years from 1991 to 2005 using two registries (Pediatric Cardiology and Dutch National Hospitalization). They found that the mean age at diagnosis was 2.1 yrs. Kim HW, Kim GB, *et al.*[12] from Division of Cardiology, Department of Pediatrics, Seoul National University Children's Hospital, studied 65 patients diagnosed with PAH between January 1985 and August 2007. They found that the mean age at the time of diagnosis was 5.7+/5.2 years This difference of age at diagnosis may be explained by the fact that these two studies were done at specialized pediatric cardiology centers where pediatric patients of all age groups were referred to whereas in our study none of the patients above 5 years of age were suspected of having PAH. This age group of 5-15 years may have reported to other cardiology centers who mostly deal with adult population.

In this study 17 cases of PAH were male and 23 female, giving a male: female ratio of 1:1.35. Almost similar results have been reported by Rich S, Dantzker DR *et al.* who collected data of 187 patients from 32 centers. They found a female preponderance with a M:F ratio of 1:1.7. A. J. Peacock *et al.*[14] retrospectively studied the epidemiological profile of 374 cases of PAH in Scotland from 1986-2001, and found a M:F ratio of 1:2. Their slightly higher female preponderance could be due to the large number of patients in their study group compared to ours. Various demographic factors were studied in relation to PAH. These included dwelling place (rural vs urban habitat), birth order, consanguinity, place of delivery and mode of delivery. None of these factors were found to have a statistically significant relation with PAH. The most common clinical features in children with PAH in this study were irritability (82.5%), tachypnea (75%) and cyanosis (70%), poor feeding (65%), followed by features of right heart failure (35%) and syncope (5%). Dantzker DR *et al.* (Rich, 1987), have reported that the most common clinical features were dyspnea (60%), fatigue (19%), and syncope (or near syncope) (13%). The higher incidence of syncope or near syncope in their study could have been due to the study population comprising of children as well as adults whereas the present study had all the patients upto 5 years of the pediatric age group. The study revealed that idiopathic PAH constituted 42.5% of the cases, 50% of the PAH cases were associated with CHD and 7.5% cases were PPHN. Our results are similar to Kim HW, Kim GB, *et al.* who found that 49.2% cases of PAH in children are associated with CHD. However

they had a low percentage of IPAH patients (16.9%) in their study. The high number of IPAH cases in this study are consistent with the results obtained by Rosa Laura E. van Loon, Marcus T.R. Roofthooft, *et al* (Rosa Laura, 2009). who found the IPAH cases to be 46% and 39.2% respectively. On echocardiography, the study revealed that the mean systolic pulmonary artery pressure in the cases of PAH was 63.17 mmHg (range: 36mmHg- 85mmHg). Most of the cases had severe PAH (65%), whereas moderate and mild PAH cases were 25% and 10% respectively. Tricuspid regurgitation was found universally in all the cases. 95% had right ventricular enlargement, 80% had associated right atrial enlargement, systolic flattening of IVS was seen in 85%, right ventricular systolic dysfunction in 70%, pulmonary regurgitation in 40%, and thickened IVS in 35%. These findings are almost similar to Eduardo Bossone, *et al*. (Eduardo Bossone, 1999) who studied the doppler echocardiographic features of 51 patients with PPH from 1992 to 1997. The majority of patients had sPAP greater than 60 mm Hg (96%) associated with systolic flattening of the interventricular septum (90%), enlarged right atrium (92%) and ventricle (98%), and reduced right ventricular systolic function (76%), thickened IVS (43%), tricuspid regurgitation (80%) and pulmonary regurgitation (31%) cases. Their study showed tricuspid regurgitation in 80% only as their cases were first evaluated by cardiac catheterization followed by doppler echocardiography whereas we used only doppler echocardiography for diagnosis of PAH in our study. The relationship of severity of PAH with age was studied. It was found 85% of severe PAH cases were in the age group of 1month to 1 year. However this association was not found to be statistically significant. This study revealed the incidence of PAH to be 18.05/10000 hospital admissions and idiopathic PAH 7.67/10000 hospital admissions. To our knowledge till date no hospital based incident studies on PAH have been done. The few incident studies which have been done have calculated the incidence in the general population from hospital based records and that too in the adult population. Only two studies till date in our knowledge have calculated the incidence of pediatric idiopathic PAH. One study done by Rosa Laura Elisabeth van Loon *et al*. (2010) in Netherlands revealed an incidence of 0.7 cases of IPAH/ million children. Other study done by S Moledina, A A Hislop, *et al*. (Moledina, 2010) recently in England calculated the incidence of idiopathic PAH in children to be 0.48 cases/million.

Taking into account the total population of children in age group of 0-15 years in Kashmir (2,001,340) as per the 2001 census (http//www.censusindia.gov.in/Tables_Published/ Basic_ Data_Sheet.aspx) we calculated the incidence of idiopathic PAH in this part of the world. This came out to be 8.49 cases per million children per year. This is significantly higher than the incidence reported by Rosa Laura Elisabeth van Loon *et al*. and S Moledina, A A Hislop, *et al* in their studies. This emphasizes the need to carry out further studies on role of possible genetic and familial factors for the high incidence of idiopathic PAH in children of Kashmir. Effective treatment modalities are needed to be employed for the large burden of idiopathic PAH cases in Kashmir to decrease the high mortality associated with this disease. Also there is need for specialized centers for early treatment of PAH associated with CHD in Kashmir to decrease the mortality associated with this potentially curable form of PAH. After applying Chi square test, only two factors were found to be statistically significant predictors of mortality in PAH in children, viz, features of right heart failure (p value .0001) and evidence of right ventricular systolic dysfunction (p value .04). Although changes in the pulmonary vasculature are the primary cause of PAH, severity of symptoms, morbidity and survival are strongly associated with right ventricular function, and right heart failure is the main cause of death in patients with PAH. Echocardiography and cardiac MRI allow noninvasive evaluation of right ventricular function. Given the importance of the right ventricle in PAH, preservation and improvement of its function are important aspects of therapy; however, there are few data specifically related to it. Simple, reproducible, noninvasive measures of right ventricular function would help to improve the management of patients with PAH, and to provide tools with which to help establish the optimal therapeutic approach to manage not only the effects of the disease on the pulmonary vasculature, but also to support and improve right ventricular function. Effective treatment modalities are needed to be employed for the large burden of idiopathic PAH cases in Kashmir to decrease the high mortality associated with this disease. Also there is need for specialized centers for early treatment of PAH associated with CHD in Kashmir to decrease the mortality associated with this potentially curable form of PAH.

Conclusion

In view of relatively higher incidence of idiopathic PAH observed in this study in children of Kashmir, further studies are needed to identify the role of possible genetic and familial factors. Effective treatment modalities are needed to be employed for the large burden of idiopathic PAH cases in Kashmir to decrease the high mortality associated with this disease.

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