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Causes of pulmonary hypertension among children.

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Abstract

Report of Pulmonary hypertension in the Arab country is limited. We carried out a retrospective chart review of all referred patients to pulmonary clinic with documented Pulmonary Hypertension based on cardiac catheterization and or Echocardiogram during 2 years period (March 2008 to February 2010). Our aim is to identify the different causes of Pulmonary Hypertension and treatment modalities in a tertiary care center in Saudi Arabia and their outcomes. A total of 114 patients with confirmed Pulmonary Hypertension. Mean age at diagnosis 3.1. 55 (48%) males, 59 (52%) females. The most common causes of Pulmonary Hypertension were: Congenital Heart Disease in 100 (87.7%) patients. Others were: Congenital anomalies in 100 (87.7%). Down Syndrome in 44 (38.5%). Unknown syndrome in 32 patients (28%). 11 patients (10%) due to congenital lung anomalies. 11 patients (10%) due to Chronic Lung Disease, 2 patients due to living in high altitude, 2 patients with obesity, 2 patients with Alagile syndrome, and 2 patients with idiopathic Pulmonary Arterial Hypertension. Factors that are related to development of Pulmonary Hypertension at presentation were: Common AtrioVentricular Canal (P value = 0.05), Obstructive sleep apnea (P value = 0.02), a female sex (P value =0.05). Factors that contributed to persistence of Pulmonary Hypertension at Follow up were: presence Congenital Heart Disease (P value=.05), unclosed Atrial Septal Defect (P value = 0.03)

Key words: Pulmonary hypertension**,** Congenital heart disease, Congenital anomalies.

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Introduction

Pulmonary arterial hypertension is defined as the mean pulmonary arterial pressures more than 25mm Hg at rest or more than 30mm Hg with exercise no matter what age (British Cardiac Society Guidelines and Medical Practice Committee, 2001), or Tricuspid regurgitation with a Doppler velocity of more than 2.5 m/sec. In pediatric patients, it is defined as systolic pulmonary artery pressure exceeds 50% of systolic systemic pressure [1-10].

Although Pulmonary hypertension related to Congenital Heart Disease shares similar lung histology with idiopathic Pulmonary Arterial hypertension, differences do exist between these etiologies. Management of Pulmonary hypertension related to Congenital Heart Disease can involve surgical correction of the cardiac defect and or treatment of the Pulmonary hypertension, depending on the underlying cardiac defect and status of disease progression. Patients with cardiac defects which result in left to right shunting are at risk of developing Pulmonary hypertension, owing to the increased shear stress and circumferential stretch induced by increased pulmonary blood flow, which leads to endothelial dysfunction and progressive vascular remodeling and, thus, increased pulmonary vascular resistance [7].

Mortality associated with Pulmonary hypertension is extremely elevated. Once diagnosis has been confirmed mean survival among adults is 2.8 years and less than 1 year among children [1-4].

Uncontrolled studies suggest that prostacyclin analogues and phosphodiesterase type 5 inhibitors may have benefits in advanced pulmonary vascular disease. Bosentan significantly reduced pulmonary vascular resistance and significantly increased 6 minute walk distance without compromising peripheral oxygen saturation, in patients with Eisenmenger's syndrome [8]. These data suggest that targeted therapies are beneficial in the Pulmonary Hypertension related to Congenital Heart Disease population [3-9].

In children, approximately 40% of cases of Pulmonary hypertension are idiopathic [10-15], around 6% are heritable,[10-15] with the remaining mainly associated with congenital heart disease and few associated with Connective

tissue diseases, Human Immunodeficiency Virus or portal hypertension [11]. A number of drugs have been approved for the treatment of Pulmonary hypertension in adults, including endothelin receptor antagonists, Prostacyclin analogues and phosphodiesterase type 5 inhibitors [5,9,12,17]. Although these drugs are used in paediatric patients [17] none have been approved for the treatment of Pulmonary hypertension in children.

In this report, we identify the different causes of pediatric pulmonary hypertension in a tertiary care center in Saudi Arabia.

Material and Methods

Retrospective chart review of Pediatric Patients, age 0 to 16 years with confirmed "Pulmonary hypertension by cardiac catheterization and or Echocardiogram studies" that were referred to pulmonary services at a tertiary care

center in Riyadh, Saudi Arabia for evaluation due to cough, recurrent chest infection and cyanosis during 2 years period Jan 2008 to Dec 2010. The later is a center for cardiac and genetic diseases referrals.

Demographic, clinical, diagnostic, morbidity and mortality data will be collected. Type of medical and, surgical interventions and their outcomes.

Only patients who had mean "pulmonary arterial pressures more than 25mmHg or Tricuspid regurgitation with a Doppler velocity of more than 2.5 m/sec or systolic pulmonary artery pressure exceeds 50% of systolic systemic pressure" are included in the study.

The study was approved by the institutional Research Advisory council.

Statistical consideration

Descriptive analysis of congenital heart diseases, value of Pulmonary Artery Pressure at presentation and Pulmonary Artery Pressure at follow up were analyzed.

Major outcome: measurements of pulmonary artery pressure from follow up Echocardiogram or cardiac catherization reports to assess improvements.

The statistical analysis of data was done by using the software package Statistical Analysis System version 9.2 (Statistical Analysis System Institute Inc., Cary, North Carolina, United States of America). Descriptive statistics for all the continuous variables are reported as mean more or less standard deviation while categorical variables are reported as frequencies and percentages. The categorical variables were compared by using Chi-square test. The statistical level of significance is set at P value less than 0.05.

Results

A total of 114 patients with confirmed Pulmonary hypertension. Mean age at diagnosis 3.1 up to 3.8 years, 55 (48%) males, 59 (52%) females. Ninety Seven (85%) are alive, 4 (3.5%) died and 13 (11.5%) lost follow up. The most common causes of Pulmonary hypertension were found to be: Congenital Heart Disease in 100 (87.7%) patients. The most common Congenital Heart Disease that caused Pulmonary Hypertension are: Atrial Septal Defect 76 (66.6%), Ventricular Septal Defect 63 (55%), Common Atrio Ventricular Canal 39 (34%), Patent Ductus Arteriosus 16 (14%), Tetralogy of Fallot in 11 patients (10%), and total anomalous pulmonary venous return in 2 patients (1.7%) (Table1). Fifty Six of 100 patients with Congenital Heart Disease had repair of their cardiac defect.

Table 1. Congenital heart disease and Pulmonary hypertension Total 100 of 114 patients (87.7%)

No.	Type of defect	Number of patients (%)
1	Atrial Septal Defect	76(66.6%)
2	Ventricular Septal Defect	63(55%)
3	Post Operative	56(49%)
4	Common Atrio Ventricular Canal	39(34%)
5	Atrial Septal Defect and Other Defect	23(20%)
6	Patent Ductus Arteriosus	16(14%)
7	Tetralogy of Fallot	11(10%)
8	Ventricular Septal Defect and Other Defect	10(8.8%)
9	Coacrtation of Aorta	10(8.8%)
10	Pulmonary Stenosis	7 (6%)
11	Patent Ductus Arteriosus and Other Defect	7 (6%)
12	Transposition of Great Arteries	5 (4%)
13	Hypoplastic Right heart	4 (3.5%)
14	Partial Anomalous Pulmonary Venous Return	3 (2.6%)
15	Hypoplastic Left heart	2 (1.7%)
16	Double Outlet Right Ventricle	2 (1.7%)
17	Total Anomalous Pulmonary Venous Return	2 (1.7%)

Table 2. *Type of congenital anomalies: Total 100 of 114 patients (87.7%)*

No	Type of Congenital anomalies	Number (%)
1	Down Syndrome	44 (38.5%)
2	Dysmorphism (Microcephaly, devel-opmental -delay, Hypotonia	32 (28%)
3	CHARGE Association	4 (3.5%)
4	Vertebral anomalies	4 (3.5%)
5	Renal Disease	3 (2.6%)
6	Scimitar syndrome	2 (1.7%)
7	Skeletal dysplasia	2 (1.7%)
8	Demyelinating Disease	1 (0.9%)

CHARGE – Choanal Atresia, Heart Defect, Anal Defect, Renal Anomalies, Genital Defect and Eye Anomalies.
€- *Patients may have combined anomalies*

Recurrent Chest Infection 41 (36%), 32 (28%) required Oxygen, Gastro esophageal reflux in 36 (32%).

Other causes of Pulmonary hypertension were: Congenital anomalies in 100 (87.7%), Down syndrome in 44(28%), Thirty-nine of 44 patients (88%) with Down Syndrome had Congenital Heart Disease.

Other congenital anomalies as Skeletal Dysplasia, CHARGE association (Choanal Atresia, Heart Defect, Anal Defect, Renal Anomalies, Genital Defect and Eye Anomalies), and 32 patients with unknown syndrome (Table 2). 11 patients (10%) due to congenital lung anomalies as Diaphragmatic hernia in association with lung hypoplasia, and congenital lobar emphysema (Table 2). 11 patients (10%) due to Chronic Lung Disease 2 patients due to living in high altitude, 2 patients with obesity, 2 patients with Alagile syndrome, and 2 patients with idiopathic Pulmonary arterial hypertension . Obstructive sleep apnea was detected on 31 (27%). Asthma 33 (30%),

Factors that affected the severity of Pulmonary hypertension more than 35 mmHg at presentations were: female sex P value less than 0.0150, and presence of congenital heart disease P value less than 0.0001. (Table 3)
Sixty Nine of 114 patients (60.5%) were started on vasodilators. Sildenafil (Revatio) was the most common drug used in 40 patients (35%). Sildenafil alone in 24 patients (35%), or in combination with Bosentan (Tracleer) in 11 patients (16%), or inhaled Ventavis (Iloprost) in 5 patients (7%).

Table 3. *Comparison Tables of Pulmonary Artery Pressurein relation to clinical condition (Total 67 patients)*

Variable	Variable 2	Less than or equal to **35** mmHg	More than 35 mmHg	Total	P value
Sex	Male	15(22.39)	15(22.39)	30 (44.78)	0.0150
	Female	8(11.94)	29(43.28)	37 (55.22)	
Congenital Heart Disease	Yes	13(19.40)	43(64.18)	56 (83.58)	<.0001
	No	10(14.93)	1(1.49)	11 (16.42)	
Atrial Septal Defect	Yes	12(17.91)	32(47.76)	44 (65.67)	0.0925
	No	11(16.42)	12(17.91)	23 (34.33)	
Ventricular Septal Defect	Yes	11(16.42)	22(32.84)	33 (49.25)	0.8658
	No	12(17.91)	22(32.84)	34 (50.75)	
Common Atrio- Ventricular Canal Defect	Yes	9(13.43)	12(17.91)	21 (31.34)	0.3205
	No	14(20.90)	32(47.76)	46 (68.66)	
Patent Ductus Arteriosus	Yes	5(7.46)	14(20.90)	19 (28.36)	0.3848
	No	18(26.87)	30(44.78)	48 (71.64)	
Obstructive Sleep Apnea	Yes	10 (14.93)	8 (11.94)	18 (26.87)	0.0266
	No	13 (19.40)	36 (53.73)	49 (73.13)	
Down Syndrome	Yes	7 (10.45)	22 (32.84)	29 (43.28)	0.1249
	No	16 (23.88)	22 (32.84)	38 (56.72)	
ASTHMA	Yes	8 (11.94)	13 (19.40)	21 (31.34)	0.6608
	No	15 (22.39)	31 (46.27)	46 (68.66)	
Recurrent Chest Infection	Yes	11 (16.42)	12 (17.91)	23 (34.33)	0.0925
	No	12 (17.91)	32 (47.76)	44 (65.67)	
OTHER Medical Condition	Yes	21 (31.34)	35 (52.24)	56 (83.58)	0.2173
	No	2 (2.99)	9 (13.43)	11 (16.42)	
Gastro Esophageal Reflux	Yes	7 (10.45)	11 (16.42)	18 (26.87)	0.6337
	No	16 (23.88)	33 (49.25)	49 (73.13)	

Bosentan was given for a total of 21 patients (18%). Bosentan alone in 6 patients (8.6%) , or in combination with Sildenafil in 14 patients (20%), or with Iloprost in one patients (1.5%). Inhaled Ventavis in a total of 8 patients (4%), Ventavis alone in 2 patients (2.8%), or in combination with Bosentan or Sildenafil in one patient (1.4%) each.

Seventy five patients (66%) continued to have Pulmonary hypertension at Follow up, and the factors that contributed to persistence of Pulmonary hypertension at Follow up were: presence Congenital Heart Disease P value

equal 0.05, un closed Atrial Septal Defect P value equal 0.03.

Discussion

Many reports have described different causes of Pulmonary hypertension in the pediatric population [18-21].

Van Loon et al. [18] described the clinical presentation of pediatric pulmonary arterial hypertension and the difficulties in how to classify pediatric Pulmonary hypertension according to the Venice classification.

There were a total of 63 children seen at a national referral center for pediatric Pulmonary hypertension underwent a diagnostic work-up for diagnosis of Pulmonary Hypertension and associated conditions and for assessment of the explanatory role of associated conditions for the Pulmonary Hypertension. Subsequently, Pulmonary ypertension was classified.

Her results showed that, Idiopathic (like) Pulmonary arterial hypertension (number equal 29; 46%), Pulmonary hypertension related to Congenital Heart Disease (number 2 equal 3; 37%), Pulmonary hypertension related Connective Tissue disease (number equal 2; 3%), Pulmonary Hypertension related disorders of respiratory system and or Hypoxemia (number equal 8; 12%), and Chronic Thromboembolic Disease related Pulmonary Hypertension (number equal 1; 2%).

Her conclusion was that Pediatric Pulmonary Hypertension frequently presented with associated conditions and syndromal abnormalities. However, detailed evaluation of this complex presentation revealed that associated conditions are not always explanatory for the Pulmonary Hypertension.

In our study, congenital heart disease was the most common cause of Pulmonary hypertension in our pediatric population with Pulmonary hypertension even in patients who had total repair of their cardiac defect (as 56/100 patients had repair). The other interesting finding is that many congenital anomalies were associated with Pulmonary hypertension specially Down syndrome in 38% of Pulmonary hypertension population, and un-known syndrome in 32 patients (28%) which is not described before with that magnitude. Also, female preponderance with Pulmonary hypertension as a factor of increasing the incidence of Pulmonary hypertension, in addition to the presence of Congenital Heart Disease at presentation (Table 3). Persistence of Pulmonary hypertension at follow up was also related to Congenital Heart Disease and unclosed Atrial Septal Defect.

Van Loon et al [22] described the outcome of a national cohort of children with

Pulmonary hypertension from 1993 to 2008, 52 consecutive children with idiopathic Pulmonary hypertension (constant number equals 29) or systemic to pulmonary shunt-associated Pulmonary hypertension (constant number equals 23) underwent baseline and follow-up assessments. Treatment was initiated depending on functional class, acute pulmonary vaso reactivity response, and drug availability.

Children for whom second-generation drugs were available had improved survival compared to their predicted survival (1, 3, and 5year survival rates 93%, 83%, and 66% versus 79%, 61%, and 50%, respectively). However, this improved survival was observed only in patients for whom second generation drugs became available during their disease course.

No improved survival was observed in patients for whom drugs were available already at diagnosis. Baseline variables associated with decreased survival included higher functional class, higher pulmonary-to-systemic arterial pressure ratio, lower cardiac index, and higher serum levels of N terminal probrain natriuretic peptide and uric acid. After start of second-generation drugs, functional class, 6 minute walking distance, and N terminal probrain natriuretic peptide improved but gradually decreased after longer follow up. Her conclusion was that the survival of pediatric Pulmonary hypertension seemed improved since the introduction of second-generation drugs only in selected patients for whom these drugs became available during their disease course. Start of second generation drugs initially induced clinical improvements, but these effects decreased after longer follow up [22].

Gatzoulis [23] mentioned that: Surgery must be performed prior to the onset of high pulmonary vascular resistance. At this stage, early changes may be reversible after correction of the cardiac defect. If surgery is delayed, it is less effective. Correction of a ventricular septal defect at age of 6 months results in normal pulmonary vascular resistance after 12 months; however, while delaying surgery until age of 2 yrs results in a reduction in resistance, normalization is not achieved [24]. It is, therefore, prudent that surgery should be very early in children with a massively increased blood flow [25].

Prostacyclin Synthase is reduced in patients with Pulmonary Arterial hypertension, resulting in inadequate production of Prostacyclin (a vasodilator with anti proliferative effects), and the Prostacyclin analogues, Epoprostenol, Treprostinil and Iloprost, have been a traditional mainstay of the treatment of idiopathic Pulmonary Arterial hypertension. There are few data for Pulmonary hypertension related to Congenital Heart Disease, but the

benefits appear to be similar. In an uncontrolled study of 20 children with Pulmonary Arterial hypertension related to Congenital Heart Disease (mean age 15 yrs), 1 yr of prostacyclin therapy improved hemodynamic and quality of life [26].

In a mixed population of 39 children with Pulmonary hypertension of various etiologies (including patients with Pulmonary hypertension related to Congenital Heart Disease, epoprostenol improved survival (84% at 3 yrs), functional status, exercise tolerance and ability to thrive. [27]. However, the intravenous delivery of these drugs is a drawback, both practically and owing to the risk of infection. Among 39 children, 38% had catheter associated problems, with 43 prescriptions for antibiotics, and 0.33 Hickman line changes per patient, per year [27].

Phosphodiesterase type 5 inhibitors, such as sildenafil and tadalafil, inhibit the degradation of Phosphodiesterase type 5, the enzyme responsible for hydrolyzing the vasodilatory cyclic guanosine monophosphate. These compounds enable vasodilation in Pulmonary Arterial hypertension, although there are limited data on their efficacy for Pulmonary Hypertension related to Congenital Heart Disease. A 12 month, open label study of children with Pulmonary hypertension (number of patients equals 14, of whom 10 exhibited Pulmonary Hypertension related to Congenital Heart Disease reported improvements in exercise capacity and haemodynamics with Sildenafil.[28] Similarly, a 6 month, prospective, open label trial of sildenafil therapy found a significant reduction in systolic and mean pulmonary artery pressures and pulmonary vascular resistance, and improved cyanosis and functional capacity, in patients with Eisenmenger syndrome [29].

A prospective, open label study of 21 patients with Pulmonary hypertension related to Congenital Heart Disease (including 15 with Eisenmenger syndrome) reported that 16 weeks' treatment with Bosentan resulted in clinical, exercise, and haemodynamic improvements.[30] Similarly, in an open label, prospective, multicentre study, Thirty three patients with Pulmonary hypertension related to Congenital Heart Disease (of whom 23 had Eisenmenger syndrome) showed improvements in functional status and exercise capacity after Bosentan treatment for a mean of 2.1 yrs [31].

Recently, a new approach to the treatment of Pulmonary hypertension related to Congenital Heart Disease has been proposed. This involves treat and repair, whereby a patient previously considered irreversible (for example with Eisenmenger syndrome) is first treated with targeted therapy to reduce their Pulmonary Arterial hypertension, before undergoing surgery to repair the cardiac defect [32]. More data are needed to determine the long term benefits and risks of this approach.

Transplantation surgery, either by heart and lung transplant or a lung transplant plus corrective cardiac surgery, is the only potentially curative option for Pulmonary hypertension- Congenital Heart Disease. This approach is, however, not without limitations. The 10yr survival for a transplanted heart/lung is around 30 to 40%, which is low compared with the expected survival of patients with Eisenmenger syndrome, making it difficult to determine optimum timing for transplant. The need for transplant might, however, be delayed by the use of targeted therapies. A retrospective study of 43 patients with Eisenmenger syndrome found that the mean time to death or inscription on the active transplant waiting list was significantly longer for those treated with prostacyclin analogues or endothelin receptor antagonists (7.8 yrs) compared with those who did not receive targeted therapy (3.4 yrs; P value equals 0.006) [32]. However, delaying the need for transplant may not be beneficial for a disease with slow progression; especially in the presence of any age restrictions for acceptance onto the transplant list. The criteria and prognostic indicators for transplant in this population are unclear and warrant consideration

In Conclusion: Congenital anomalies are common association with Pulmonary hypertension in the pediatric population. Further studies are needed to identify the role in the progression of Pulmonary Arterial Hypertension.

In summary

Pulmonary hypertension is a common disease and should be diagnosed and treated early before it becomes resistant to vasodilators. Early closure of Congenital Heart defect improves Pulmonary Hypertension.

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