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Pulmonary Hypertension (PHT) in Patients with Down Syndrome: The Experience in a Tertiary Care Center in Saudi Arabia

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Abstract

Children with Down syndrome (DS) have an increased risk for developing pulmonary hypertension due to multiple factors, including the presence of congenital Heart disease with persistent left-to-right shunts, chronic upper airway obstruction or abnormal pulmonary vasculature growth.

Objectives: To identify the possible contributing factors of PHT in patients with Down syndrome, and identify the role of management intervention in improving PHT.

Methods: Retrospective chart review for all Down syndrome patients that were referred to pulmonary services at a tertiary care center-Riyadh, Saudi Arabia with confirmed pulmonary hypertension (PHT) by Echocardiogarm (Echo) and or cardiac catheterization during the period 1998-2008. Demographic, clinical data, type of cardiac defect, use of vasodilator, diagnostic tests, morbidity, and mortality data were collected.

Results: A total of 59 patients (pts) with DS 34 (58%) Male, 25 (43%) female. 39 (66%) pts are alive, 14 (24%) died, and 6 (10%) are lost follow up (FU). Age at diagnosis was 3.3 ± 3.9 yrs. Age at FU 9 ± 5.9 yrs. 46 pts (78%) had cardiac defects. 35/46 pts (76%) required cardiac repair at age of 2.6 ± 3.9 yrs. 44/59 (75%) Pts had PHT at diagnosis at Age of 3.2 ± 4 yrs. 10 pts, their PHT progressed, and 9 remained within the same degree. 33 (56%) pts of the total DS group continued to have PHT at FU. 28 (47%) pts had signs and symptoms with obstructive sleep apnea (OSA). 45 pts (76%) were treated for asthma symptoms. 35 (59%) for chest infection. 41 pts (69%) required home O2 during their FU. 26 (44%) pts had radiological signs of gastroesophageal reflux (GER. 20 Pts (34%) had neurological problem as cerebral palsy and Seizures.

It was found that DS pts with cardiac defects were more prone to develop PHT and OSA than those who do not have cardiac defects (P=0.05). Chest infection was more common in DS patients with PHT compared to those DS without PHT.

Conclusion: Pulmonary hypertension is common in Down's syndrome patients with or without cardiac defects. Factors that may contribute to development of PHT in our population were: OSA, asthma and GER. These factors should screen for routinely in such patients.

Keywords: Down syndrome; Congenital heart disease; Arab; Pulmonary hypertension

Introduction

Children with Down syndrome (DS) have an increased risk for developing pulmonary hypertension (PHT) due to multiple factors [1]: Congenital heart disease with persistent left-to-right shunts [2], chronic upper airway obstruction [3], abnormal pulmonary vasculature growth [1-4], alveolar hypoventilation [3,5,6], pulmonary tissue damage [7], recurrent Pulmonary infections [7], a thinner media of the pulmonary arterioles [7,8], a diminished number of alveoli which aggravate Pulmonary vascular disease (PVD) [1,2,4,7,8].

In another report, the increased incidence of Down Syndrome and Persistent pulmonary hypertension (PPHT) was thought to be due to an intrinsic factors such as: Abnormal production of NO [9], low pulmonary vasodilation response to [10], detection of Bone morphogenic protein (BMPR) mutation occurrence in a subset of DS patients with congenital heart disease and PHT [11-13].

Many studies have tried to calculate the incidence of PHT in DS patients [1-4].

A retrospective study of DS patients was carried out during a 3-year admission period to the neonatal intensive care unit, Columbus children hospital, in the state of Ohio [1]. The incidence of PPHN was significantly lower versus the incidence of PPHN in DS ($z = 2.7$, $p = 0.007$). It was concluded that DS patients have an increased incidence of PPHN (10 times) compared to historical controls of the pediatric population regardless of baseline demographics [1]. Their conclusion was that: Aggressive early (after 2-4 weeks of postnatal age when pulmonary vascular resistance has subsided) treatment of shunts and attention to factors aggravating pulmonary hypertension such as upper airway obstruction and hypoxia from chronic lung disease results in resolution of pulmonary hypertension [1].

In another study [4], 17 infants with DS without structural Congenital heart disease (CHD) who presented with persistent PHT

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in the newborn period. Respiratory distress with or without hypoxia was the presenting feature in these infants. PHT resolved in the majority of the survivors. 2 infants with refractory PHT benefited from PDA ligation. Autopsies in 2 infants demonstrated structural lung immaturity. The author suggested that infants with Down syndrome are at risk of developing persistent pulmonary hypertension even in the absence of structural heart disease and these infants should be followed up until resolution of the pulmonary hypertension [4].

Congenital cardiac defects are reported in 19–43% of cases [14]. The most common lesion is an endocardial cushion defect in 43%, Ventricular septal defect (VSD) in (32%), Atrial septal defect (ASD) in (10%), Tetralogy of Fallot (TOF) in (6%) and isolated Patent ductus arteriosus (PDA) in (4%). In 1/3 of cases have multiple cardiac defects [11]. DS and CHD seem to develop PHT at a faster rate and have persistent disease after cardiac surgery compared to non-DS patients with similar defects [2].

The first 6 months of life is considered to be the best time for definitive repair in view of the progression of pulmonary vascular disease (PVD) and atrioventricular valve regurgitation. Some patients with Down's syndrome undergo successful repair even in their second decade and others die of PH crisis even in their first 6 months of life [15].

Upper airway obstruction is common in DS due to midfacial hypoplasia, Macroglossia, narrowing of the nasopharynx, tonsillar and adenoidal enlargement, lingual tonsils, Choanal stenosis, shortening of the palate, subglottic stenosis, laryngomalacia, Tracheomalacia and congenital malformations of the larynx, trachea [7].

The incidence of OSA was reported to be at a range of 30-50%. Exacerbating factors including obesity and gastro-esophageal reflux may contribute to the occurrence of sleep apnoea [7]. Many reports on Polysomnography studies in DS [6,16-21] have shown that 50-100% of patients have respiratory sleep disturbance. Untreated OSA results in serious morbidities including failure to thrive, pulmonary hypertension (PHT), poor academic performance, and deterioration in mental function [6,16-21].

Pulmonary arterial hypertension (PAH) may develop as a consequence of a systemic-to pulmonary shunt. Increased pulmonary vascular resistance may ultimately lead to a reversal of the systemic-to-pulmonary shunt leading to cyanosis, the so called "Eisenmenger's syndrome". Once the Eisenmenger's syndrome has occurred, repair of the underlying defect is contraindicated. The right ventricle will be unable to cope with the progressively increased afterload due to the high pulmonary vascular resistance and will fail [22-27]. Dyspnea, arrhythmia and premature death are common features of PAH [22-27].

The BREATHE-V [28] study showed that Bosentan is safe and well tolerated in patients with Eisenmenger's syndrome without any worsening of pulmonary-to-systemic shunting [28]. However, in down patients with Eisenmenger's syndrome, the therapeutic role of Bosentan is not known, as patients with Down syndrome were generally not included in these studies.

The aim of this study is to review the different causes of pulmonary hypertension in patients with Down syndrome and its suggested management and review our experience in a tertiary care center in Saudi Arabia.

Material and Methods

A retrospective chart review for all DS patients (Pts) referred to pulmonary service for respiratory evaluation due to cough, recurrent chest infection and cyanosis during the period 1993-Dec 2008. Patients were referred from all Pediatric subspecialties from the same hospital either as in-patient or as out-patient services. During the same period there were 800 patients diagnosed with Down syndrome in the hospital, but only 59 patients were referred for respiratory evaluation. Our hospital is a tertiary care center and the main referral center for genetic and cardiac diseases.

Once the patient is seen by the Pulmonologist, a complete clinical evaluation with laboratory and radiological evaluations including: Chest and neck x-rays to evaluate upper air way obstruction. Complete blood count, liver enzymes and complete immunological workup. Echo cardiogram evaluation and referral to Pediatric cardiology once PHT is diagnosed for possible cardiac catheterization.

PHT was defined as pulmonary artery pressure (PAP) on cardiac catheterization and or Echo studies to be >50% of systolic systemic pressure. Demographic, clinical, diagnostic, morbidity and mortality data were collected.

Statistical consideration: Descriptive analyses of congenital heart diseases, value of pulmonary artery pressure (PAP) at presentation and PAP at follow up were analyzed.

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

The statistical analysis of data was done by using the software package SAS version 9.2 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics for all the continuous

Variable	Number (%)
Sex :	
Male	34 (57.6)
Female	25 (42.3)
Prematurity	7 (11.8)
Status:	
Alive	39 (66)
Died	14 (24)
Lost Follow up	6 (10)
Cardiac defect:	
Yes	46 (78)
No	13 (22)
Type of cardiac defect: out of 46 patients	
Atrial septal defect (ASD)	16 (27)
Ventricular septal defect (VSD)	8 (13.5)
Common A-V canal	18 (30.5)
Patent ductus arteriosus (PDA)	3 (5)
Others	2 (3.5)
Multiple defects	21 (46%)
No cardiac defect	12 (20.5)
Obstructive sleep apnea	28 (47)
Tonsillectomy	20 (34)
Tracheostomy	4 (7)
Asthma	45 (76)
Recurrent chest infection	35 (59%)
Home Oxygen	41 (69)
Gastroesophageal reflux	26 (44)
Nissen-fundoplication	12 (20)
Celiac disease	7 (12)
Hypothyroidism	23 (39)
Neurological diseases (cerebral palsy, Seizures)	20(34)
Associated diseases (skin and eye problems)	41(69)

Table 1: Down syndrome and disease associations.

Variable	PHT Yes	PHT No	P value
Prematurity			
Yes	7	0	0.09
No	37	15	
Cardiac defect			
Yes	37	9	0.05
No	7	6	
OSA			
Yes	19	9	0.2
No	25	6	
Hypothyroidism			
Yes	18	5	0.6
No	26	10	
Neurological disease			
Yes	13	7	0.2
No	31	8	
Asthma			
Yes	42	15	0.4
No	2	0	
Chest Infection			
Yes	37	8	0.01
No	7	7	
GER			
Yes	22	4	0.1
No	22	11	

PHT- Pulmonary hypertension
OSA- Obstructive sleep apnea

Table 2: Factors affect (PHT) development in patients with Down syndrome.

variables are reported as mean ± 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 $p < 0.05$

Results

A total of 59 patients (pts), with DS (Table 1) Patients were followed for a period of 5.6 ± 4.8 years (yrs). Age at diagnosis was 3.3 ± 3.9 years. Age at follow up (FU) 9 ± 5.9 yrs.

Forty six pts (78%) had cardiac defects (Table 1), and 21 (46%) had multiple defects. 35/46 pts (76%) required cardiac repair at age of 2.6 ± 3.9 yrs.

Forty four of 59 pts (75%) had PHT at diagnosis at Age of 3.2 ± 4 yrs, 13 (22%) mild type, 12 pts (20%) moderate, 19 pts (33%) had severe PHT.

Ten patients, their PHT progressed, 9 remained within the same degree. 33 (56%) pts of the total DS group continued to have PHT at FU.

A total of 5 patients out of 44 who were diagnosed with PHT received vasodilators. All 5 patients had cardiac catheterization before they received the treatment. One patient with common AV canal and PDA had Eisenmenger's syndrome and improved on Bosentan (from Functional "FC" IV → II) and 6 minute walk test (MWT) from 30% → 75% after 6 months of treatment. Another patient with ASD, VSD, Asthma and Obesity with FC III, improved on Bosentan to FC II. Three pts with post repair of common A-V canal improved on Sildenafil. The remaining 39 patients with PHT did not receive any treatment at the time of the study.

Factors that were associated with PHT at diagnosis were found to be: cardiac defects (P=0.05), and recurrent chest infection ($p<0.01$) (Table 2).

Cardiac defect in patients with DS may increase the risk of developing PHT compared to those that did not have CHD (P= 0.05) (Table 3).

Patients with DS and cardiac defect are more prone to develop obstructive sleep apnea compared to those who did not have cardiac defect (p= 0.01) (Table 2).

Discussion

In patient with Down syndrome, PAH has been suggested to develop earlier and to have a more violent course [1-8]. Eisenmenger syndrome carries a high risk of morbidity in a relatively young patient population and has limited therapeutic options [1-8]. Once the Eisenmenger syndrome has occurred, repair of the underlying defect is contraindicated. The right ventricle will be unable to cope with the progressively increased after load due to the high pulmonary vascular resistance and will fail [8]. Dyspnoe, arrhythmia and premature death are common features of PAH [1-9]. Exercise tolerance and quality of life in patients with PAH related to congenital heart disease has been shown to be low [1-15].

Prostacyclin Synthase is reduced in patients with PAH, resulting in inadequate production of prostacyclin I2 (a vasodilator with anti proliferative effects), and the prostacyclin analogues, epoprostenol, treprostinil and iloprost, have been a traditional mainstay of the treatment of idiopathic PAH. There are few data for PAH-CHD, but the benefits appear to be similar. In an uncontrolled study of 20 children with PAH-CHD (mean age 15 yrs), 1 yr of prostacyclin therapy improved hemodynamic and quality of life [29].

In a mixed population of 39 children with PAH of various etiologies (including patients with PAH-CHD), 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,

Variable	Cardiac Yes	Defect No	P value
OSA			
Yes	18	10	0.01
No	28	3	
Asthma			
Yes	45	12	0.3
No	1	1	
Chest Infection			
Yes	36	9	0.4
No	10	4	
GER			
Yes	23	3	0.08
No	23	10	
Oxygen			
Yes	28	7	0.6
No	18	6	
PHT			
Yes	37	7	0.05
No	9	6	

OSA- Obstructive sleep apnea
GER- Gatrso-esophageal reflux
PHT- Pulmonary hypertension

Table 3: cardiac defect and disease association in patients with Down syndrome.

38% had catheter-associated problems, with 43 prescriptions for antibiotics, and 0.33 Hickman line changes per patient, per year [30].

Phosphodiesterase type-5 (PDE-5) inhibitors, such as sildenafil and tadalafil, inhibit the degradation of PDE-5, the enzyme responsible for hydrolyzing the vasodilatory cyclic guanosine monophosphate. These compounds enable vasodilation in PAH, although there are limited data on their efficacy for PAH-CHD. A 12-month, open-label study of children with PAH (n514, of whom 10 exhibited PAH-CHD) reported improvements in exercise capacity and haemodynamics with sildenafil [31]. 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 (n57) [32].

A prospective, open-label study of 21 patients with PAH-CHD (including 15 with Eisenmenger syndrome) reported that 16 weeks' treatment with Bosentan resulted in clinical, exercise, and haemodynamic improvements [33]. Similarly, in an open label, prospective, multicentre study, adults with PAH-CHD (n533, of whom 23 had Eisenmenger syndrome) showed improvements in functional status and exercise capacity after bosentan treatment for a mean of 2.1 yrs [34].

Recently, a new approach to the treatment of PAH-CHD 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 PAH, before undergoing surgery to repair the cardiac defect [35]. More data are needed to determine the long-term benefits and risks of this approach.

Transplantation surgery, either by heart/lung transplant or a lung transplant plus corrective cardiac surgery, is the only potentially curative option for PAH-CHD. This approach is, however, not without limitations. The 10-yr survival for a transplanted heart/lung is around 30–40%, 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; p50.006) [36]. 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 our study, we have shown that congenital heart disease is common in patient with DS and PHT is a common association in those with cardiac defect and may cause progressive disease and early death. Once vasodilators became available in our center and started to be used, it showed definite improvement of clinical status in some patients.

Our study is limited in that most of the referred patients had already respiratory symptoms which might reflect the severity of their disease and mildly symptomatic patients might have been escaped from being fully investigated for PHT. And accordingly it may have affected our statistical analysis.

Summary

PHT is common in DS pts with or without cardiac defects. Physician should be aware of other factors that may cause PHT such as: OSA, asthma and GER. Vasodilators may have favorable effect in DS with un-repaired cardiac defects. The survival and quality of life have been improving in patients with DS due to early repair of congenital heart defects to halt the progression of PAH, and improvement in critical care facilities and early vasodilator use.

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