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 Echocardiogram (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).

Conclusions: 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 arteries [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...
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 cardogram 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) |
| Tonsillctomy | 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.
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.

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 ± 3.9 years. Seventeen (30%) pts of the total DS group continued to have PHT at FU.

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.

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

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

PHT- Pulmonary hypertension  
OSA- Obstructive sleep apnea

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).

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,
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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