MINI REVIEW

Down's Syndrome and Pulmonary Arterial Hypertension

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Children with Down's syndrome (DS) are at an increased risk of developing pulmonary arterial hypertension (PAH) due to multiple factors: congenital heart disease (CHD) with persistent left-to-right shunts, chronic upper airway obstruction, abnormal pulmonary vasculature growth, alveolar hypoventilation, and recurrent pulmonary infections. Congenital cardiac defects are reported in 19–43% of cases. With the common lesion is an endocardial cushion defect in 43%. DS and CHD seem to develop PAH at a faster rate and have persistent disease after cardiac surgery compared to non-DS patients with similar defects. The upper airway obstruction is common in DS due to midfacial hypoplasia, macroglossia, narrowing of the nasopharynx, tonsillar and adenoidal enlargement, laryngomalacia, tracheomalacia, and congenital malformations of the larynx and trachea. The incidence of OSA was reported to be in a range of 30–50%. Exacerbating factors including obesity and gastroesophageal reflux may contribute to the occurrence of sleep apnea. In this report, I review the causes of pulmonary hypertension in this population, and its management.

Keywords: Down's syndrome, pulmonary hypertension, congenital heart disease

INTRODUCTION

Children with Down's syndrome (DS) are at an increased risk of developing pulmonary hypertension (PAH) due to multiple factors:[1] congenital heart disease (CHD) 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] and a diminished number of alveoli.[1,2,4,7]

In an autopsy study of six patients with DS,[2,9] it was found that there was a reduction in the alveolar count, persistence of the fetal double capillary network in the lung, and a reduction in the cross-sectional area of the vascular bed.[2,9]

In DS and associated cardiac malformations, the number of airway generations was reduced by 25% or more than expected.[10-12]

The increased incidence of DS and persistent pulmonary hypertension (PPHT) was thought to be due to intrinsic factors such as abnormal production of NO but respond appropriately to exogenous NO,[13] less pulmonary vasodilation response to NO in DS patients versus controls in the cardiac catherization laboratory,[14] detection of bone morphogenic protein (BMPR2) mutation occurrence in a subset of DS patients with CHD and PHT.[15-17]

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INCIDENCE[1]

In order to determine if the incidence of persistent pulmonary hypertension of the newborn (PPHN) is also higher in neonatal DS patients compared to the general population. 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. DS patients with the meconium aspiration syndrome, pulmonary infections, or pulmonary space-occupying lesions were excluded. DS patients were divided into four groups based on treatment and consisted of no intervention (A), supplemental oxygen (B), mechanical ventilation use (C), and inhaled nitric oxide administration (D). Group D was defined as having PPHN. A total of 58 patients were with DS. Twenty-four DS patients were in group A, 17 in group B, 10 in group C, and 7 in group D. There was no difference between the four groups for gender (males: 10, 5, 5, and 5, respectively), gestational age (36.4, 38.2, 36.4, and 36.4 weeks, respectively), weight (2.8, 3.0, 2.4, and 3.0 kg, respectively), or the presence of congenital heart defects (17, 10, 6, and 1, respectively). The estimated number of DS patients born in the state of Ohio during that period was 598; therefore, the incidence of PPHN in DS was 1.2%. The reported incidence of PPHN was 0.1%. The reported incidence of PPHN was significantly lower versus the incidence of PPHN in DS ($z = 2.7$, $P = .007$). 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]

In another study, the author identified 17 infants with DS without structural CHD who presented with persistent pulmonary hypertension in the newborn period. Respiratory distress with or without hypoxia was the presenting feature in these infants. Pulmonary hypertension resolved

in the majority of the survivors. Two infants with refractory pulmonary hypertension benefited from patent ductus arteriosus ligation. Autopsies in two infants demonstrated structural lung immaturity. The author suggested that infants with DS are at a risk of developing persistent pulmonary hypertension even in the absence of structural heart disease and these infants should be followed up until the resolution of the pulmonary hypertension.[4]

DS AND CARDIAC DISEASES[18]

Congenital cardiac defects are reported in 19–43% of cases. The most common lesions are: an endocardial cushion defect in 43%, VSD in (32%), ASD in (10%), TOF in (6%), and isolated PDA in (4%). One-third of cases had multiple cardiac defects.[18] 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]

In a study aimed to determine the vascular bed in DS, sixty-nine children with DS, with an atrial-septal defect, patent ductus arteriosus, ventricular septal defect, or endocardial cushion defects, and 315 children with similar cardiac anomalies without this syndrome underwent cardiac catherization during an 8-year period. Only patients under 17 years of age were included in this study. Nine-tenths of the children with DS but only one-fourth of the control group had abnormally high pulmonary arterial pressures. Nine of 11 children with defects of the atrial septum and DS had pulmonary hypertension; in contrast, only 5 of 55 control subjects with similar defects had pulmonary hypertension. The author suggested that children with CHD and DS have an unusually high pulmonary vascular resistance and a propensity for an early development of severe damage to the pulmonary vascular bed.[18]

The first 6 months of life are considered to be the best time for a definitive repair in view of the progression of PVD and atrioventricular valve regurgitation. Some patients with DS undergo a successful repair even in their second decade and others die of PH crisis even in their first 6 months of life.[19]

Patients with DS undergoing CHD repair had an acceptable postoperative morbidity and low mortality. Their results are comparable to non-DS cardiac patients. From an ICU perspective, the majority of these patients do well postoperatively with a good ICU outcome.[20]

DS AND INFECTIONS

DS individuals have a higher rate of infections, especially respiratory tract infections (RTI) which are 50 times more common compared to the general population.[7] Bronchopneumonia a common cause of death with a mortality rate 124 times that of the general population.[21,22]

An increase in infections attributed to a variety of factors such as environmental exposure, reduced mobility, CHD, and abnormal pulmonary vasculature.[23]

Abnormal immunological functions were reported due to B-, T-, and natural killer cell functional abnormalities, and in cytokine production, in phagocytic and chemotactic responses, and in immunoglobulin levels with reduced levels of lymphocytes. An impaired T-cell function is associated with low CD4 numbers.[24]

Autoimmune disease occurs with antithyroid, antigliadin, and anticardiolipin antibodies and a worsening immunoglobulin function with age.[25]

DS AND UPPER AIRWAY OBSTRUCTION

Upper airway obstruction (OSA) 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 and trachea.[7]

The incidence of OSA was reported to be in a range of 30–50%. Exacerbating factors including obesity and gastroesophageal reflux may contribute to the occurrence of sleep apnea.[7]

In one study, four infants with DS developed cor pulmonale and heart failure in association with the chronic upper airway obstruction.[5] Features of the sleep apnea syndrome were conspicuous, namely, noisy breathing with retraction, cyanosis and frequent apnea during sleep, and daytime lethargy and somnolence. The clinical picture masqueraded as cyanotic CHD. Arterial blood gas analyses revealed alveolar hypoventilation, especially during sleep. The nature of the obstructive element was variable. Adenoidectomy provided partial relief in one patient, and tonsillectomy and adenoidectomy resulted in a temporary improvement in two others. Three patients were markedly benefited by tracheostomy. The functional inspiratory pharyngeal closure was demonstrated fluorographically in one patient.

Infants with DS may be predisposed to upper airway obstruction by virtue of hypoplasia of facial and oropharyngeal structures and generalized hypotonia. Additional obstructive elements may be contributed by hypertrophied lymphoid tissue, excessive secretions, and glossoptosis. The removal of the obstructive element is helpful, but functional obstruction may only be relieved by tracheostomy.[5]

In an effort to identify the type of respiratory disturbances during sleep in DS, a study was conducted that included 23 children with DS, compared with 13 children with primary snoring.[6] All underwent a 6- to 8-h sleep study. The results showed that the respiratory disturbance index was significantly higher in the children with DS (2.8 ± 2.3 events/h vs. 0.6 ± 0.4 events/h, $P < .05$). Sleep was significantly fragmented in children with DS, who had a significantly higher arousal/awakening (A/Aw) index (24.6 ± 7.9 events/h) compared with the comparison group (17.6 ± 4.0 events/h) ($P < .02$). A higher percentage of jerks associated with A/Aw and respiratory event-associated A/Aw was observed in patients with DS (45.2% ± 25% and 8.6% ± 6.4%, respectively) compared with the control patients (10.2% ± 4.5% and 1.5% ± 2.1%) ($P < .02$). The median length of occurrences of stage 2 sleep was 27% shorter in the DS group ($P < .03$). The number of shifts from "deeper" to "lighter" stages of the nonrapid eye movement sleep was 30% greater ($P < .02$) in the DS group. The author concluded that children with DS have significant sleep

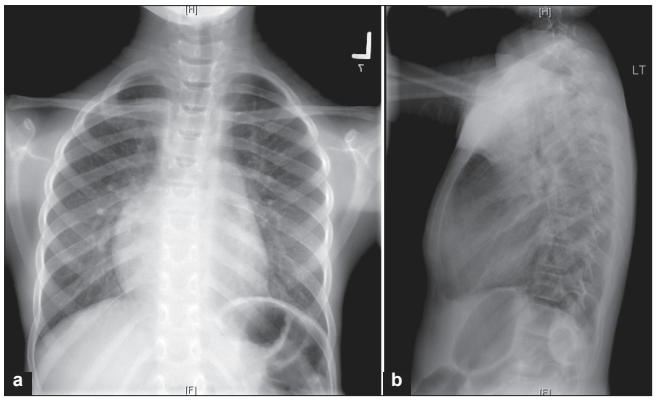

Figure 1 a and b: Chest x ray AP + lateral views of a patient with Down's syndrome and Eisenmenger's syndrome showing mild cardiomegaly, mild shifting of the heart to the right side due to mild right convex scoliosis and enlargement of pulmonary blood vessels

fragmentation, manifested by frequent awakening and arousals, which are only partially related to the obstructive sleep apnea syndrome. Residual symptoms of UAO are common after surgery. A comprehensive and individualized approach is important in the management of UAO in DS.[6]

EISENMENGER'S SYNDROME IN DS

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. In patients with DS, PAH has been suggested to develop earlier and to have a more violent course.[26] Eisenmenger's syndrome carries a high risk of morbidity in a relatively young patient population and has limited therapeutic options.[27] Once the Eisenmenger's syndrome has occurred, the 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.[27] Dyspnea, arrhythmia, and premature death are common features of PAH [Figures 1 and 2].[27,28]

Exercise tolerance and quality of life in patients with PAH related to congenital heart disease have been shown to be low.[28] New medical treatment strategies, such as prostacyclin, endothelin receptor antagonists (Bosentan), and phospho-diesterase.

5-inhibitors have substantially improved the clinical status and life expectancy of patients with PAH.[29] The BREATHE-V study showed that Bosentan is safe and well tolerated in patients with Eisenmenger's syndrome without any worsening of pulmonary-to-systemic shunting.[29-31] However, in DS patients with Eisenmenger's syndrome, the therapeutic role of Bosentan is not known, as patients with DS were generally not included in these studies.

Data on Bosentan treatment in DS patients with Eisenmenger's syndrome[28] were found in one open-label study; 24 DS patients (>18 years of age) with Eisenmenger's syndrome (17 males) were treated with Bosentan. Their mean age was 38 years (range 19–55 years). All DS patients were evaluated at baseline and during

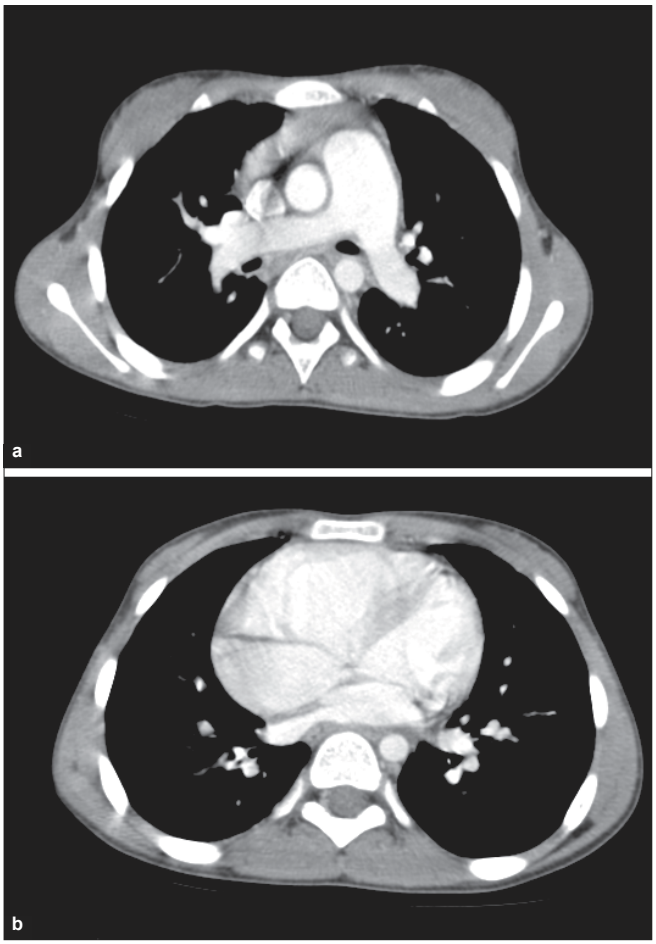

Figure 2: CT chest of the same patient in Figure 1, Down's syndrome with Eisenmenger's syndrome showing enlarged pulmonary trunk and main pulmonary arteries (a) and significantly enlarged right atrium and right ventricle (b)

follow-up with laboratory tests, 6-min walk test (6-MWT), Doppler echocardiography, and quality-of-life questionnaires. The median follow-up of DS patients treated with Bosentan was 11.5 months (range 3–23 months). The induction of oral Bosentan therapy was well tolerated among all 24 DS patients. No serious drug reactions were noted. Median 6-MWT increased from 296 m (range 84–459 m, $P < .05$) after 12 weeks. After 26 and 52 weeks of treatment with Bosentan, the median 6-MWT distance was 276 m (range 140–462 m, $n = 15$, $P = .6$) and 287 m (range 131–409 m, $n = 7$, $P = .3$), respectively. Quality-of-life questionnaires scores remained stable during treatment. The author concluded that patients with DS may benefit from Bosentan treatment when they have Eisenmenger's syndrome. Medical treatment appears to be safe and the treatment effects do not deviate from those observed in Eisenmenger's syndrome patients without DS.[28]

CONCLUSION

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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