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Causes of Pulmonary Arterial Hypertension in Down's Syndrome

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Children with Down syndrome (DS) have an increased risk for developing pulmonary arterial hypertension (PAH) due to multiple factors: Congenital heart disease with persistent left-to-right shunts, chronic upper airway obstruction, abnormal pulmonary vasculature growth, alveolar hypoventilation and recurrent pulmonary infection.

Congenital cardiac defects are reported in 19-43% of Down's syndrome. 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.

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 the trachea. The incidence of OSA was reported to be 30-50%. Exacerbating factors including obesity and gastro-esophageal reflux may contribute to the occurrence of sleep apnea.

The aim of this paper is to review the causes of pulmonary hypertension in DS population and its management.

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Children with Down's syndrome (DS) have an increased risk of developing pulmonary hypertension (PAH) due to multiple factors: Congenital heart disease with persistent left-to-right shunts, chronic upper airway obstruction, abnormal pulmonary vasculature growth, alveolar hypoventilation, pulmonary tissue damage, recurrent pulmonary infections, a thinner media of the pulmonary arterioles, a diminished number of alveoli could also aggravate pulmonary vascular disease (PVD)[1-8].

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

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

In another report, the increased incidence of Down's syndrome and persistent pulmonary hypertension (PPHT) was thought to be due to intrinsic factors such as abnormal production of NO but it responds appropriately to exogenous NO, less pulmonary vasodilation response to NO in DS patients versus controls in the cardiac catheterization laboratory, detection of Bone Morphogenic Protein (BMPR2) mutation occurrence in a subset of DS patients with congenital heart disease and PHT[13-17].

INCIDENCE[1]

To determine if the incidence of persistent pulmonary hypertension of the newborn (PPHN) is higher in neonatal DS patients compared to the general population, a retrospective study of DS patients was carried out during 3 year admission period to the neonatal intensive care unit, Columbus children hospital, in the state of Ohio. DS patients with 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) inhaled nitric oxide administration, D) was defined as having PPHN. Fifty-eight patients with DS were found, 24 DS patients were in group A, 17 in group B, 10 in group C, and 7 in group D. There was no gender difference between the four groups (males: 10, 5, 5, and 5, respectively), gestational age was 36.4, 38.2, 36.4, and 36.4 weeks, respectively, weight was 2.8, 3.0, 2.4, and 3.0 kg, respectively and the presence of congenital heart defects was 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 is 0.1%. The Reported 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].

In another study, the author identified 17 infants with Down syndrome without structural congenital heart disease 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 Down syndrome are at risk of developing persistent pulmonary hypertension even in the absence of structural heart disease and these infants should be followed until resolution of the pulmonary hypertension[4].

DS and Cardiac Diseases[18]

Congenital cardiac defects are reported in 19-43% of cases. The common lesion is an endocardial cushion defect in 43%, VSD in 32%, ASD in 10%, TOF in 6% and isolated PDA in 4%. One-third of cases have multiple cardiac defects[18]. DS and congenital heart disease (CHD) seem to develop PHT at a fast 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 Down Syndrome (DS), sixty-nine DS children had atrial-septal defect, patent ductus arteriosus, ventricular septal defect, or endocardial cushion defects and 315 children with similar cardiac anomalies without DS underwent cardiac catheterization during an 8-years period. Only patients under 17 years of age were included in this study. Nine-tenths of the children with Down syndrome and one-fourth of the control group had abnormally high pulmonary arterial pressures. Nine of 11 children who had defects of the atrial septum and Down syndrome had pulmonary hypertension, in contrast, only 5 of 55 control subjects with similar defects had pulmonary hypertension. The author suggested that children with congenital heart disease and DS have an unusually high pulmonary vascular resistance and a propensity for early development of severe damage to the pulmonary vascular bed[18].

The first six months of life is considered the best time for definitive repair because of the progression of 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 six months of life[19].

Patients with Down's syndrome undergoing CHD repair had an acceptable postoperative morbidity and low mortality. Their results are comparable to non-down's cardiac patients. From an ICU perspective, most of these patients do well postoperatively with good ICU outcome[20].

DS and Infections

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

Increase in infections attributed to a variety of factors such as environmental exposure, reduced mobility, congenital heart disease, abnormal pulmonary vasculature[23].

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

Autoimmune disease occurs with anti-thyroid, antigliadin and anticardiolipin antibodies and worsening immunoglobulin function with age[25].

DS and Upper Air Way Obstruction (OSA)

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 and trachea[7].

The incidence of OSA was reported to be 30-50%. Exacerbating factors including obesity and gastro-esophageal reflux may contribute to the occurrence of sleep apnoea[7].

In a study, four infants with Down syndrome developed cor pulmonale and heart failure in association with 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 congenital heart disease. Arterial blood gas analysis 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 temporary improvement in two others. Three patients were markedly benefited by tracheostomy. Functional inspiratory pharyngeal closure was demonstrated fluorographically in one patient.

Infants with Down syndrome may be predisposed to upper airway obstruction by virtue of hypoplasia of facial and oropharyngeal structures and generalized hypotonia. Hypertrophied lymphoid tissue, excessive secretions and glossoptosis may contribute additional obstructive elements. 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 of 23 children with DS, compared with 13 children with primary snoring, all underwent 6- to 8 hour sleep study[6]. The result showed that **t**he respiratory disturbance index was significantly higher in the children with DS (2.8 ± 2.3 events/h verses 0.6 ± 0.4 events/hr, $p < .05$). 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 control 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 occurrence of stage 2 sleep was 27% shorter in the DS group ($p < .03$). The number of shifts from “deeper” to “lighter” stages of non-rapid eye movement sleep was 30% greater ($p < .02$) in the DS group. The author concluded that children with DS have significant sleep fragmentation, manifested by frequent awakening and arousals, which are only partially related to 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 because of 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 Down's syndrome, PAH has been suggested to develop earlier and to have 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, 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 eventually will fail [27]. Dyspnea, arrhythmia and premature death are common features of PAH[27,28].

Exercise tolerance and quality of life in patients with PAH related to congenital heart disease has 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; patients with Down syndrome were generally not included in these studies.

Data on Bosentan treatment in Down syndrome patients with Eisenmenger's syndrome was found in one open-label study, 24 DS patients (>18 years) with Eisenmenger's syndrome (17 males) were treated with Bosentan[28]. Their mean age was 38 years (range 19-55 years). All DS patients were evaluated at baseline and during follow-up with laboratory tests; six minutes walk test (6-MWT), Doppler echocardiography, and quality of lie questionnaires. The median follow-up of DS patients treated with Bosentan was 11.5 months (range 3-23 months). 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, $p<0.05$) after 12 weeks. After 26 and 52 weeks of treatment with Bosentan, median 6-MWT distance was 276 m (range 140-462 m, n=15, $p=0.6$) and 287 m (range 131-409m, n=7, $p=0.3$), respectively. Quality of life questionnaires scores remained stable during treatment. The author concluded that patients with Down syndrome 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 patients without Down syndrome[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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