Comprehensive Evaluation and Ongoing Approach to Children With Down Syndrome Who Have Pulmonary Hypertension or Are at Risk of Developing Pulmonary Hypertension

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Children with Down syndrome and pulmonary hypertension (PH) are a unique and challenging group of patients. Down syndrome, or Trisomy 21, affects approximately one in every 600 to 800 live births.¹ PH, currently defined as a resting mean pulmonary artery pressure of ≥ 25 mm Hg, is known to increase morbidity and mortality significantly in this group of patients and has been identified in as many as 28% of all patients with Down syndrome. Furthermore, specific risk factors and comorbidities have been shown to increase the chance of developing PH in this population.² Careful screening and proper treatment is imperative in children with Down syndrome to prevent the development, recurrence, or progression of PH in this population.

Recent findings from Bush et al demonstrate clear clinical characteristics and risk factors for development of PH in children with Down syndrome.² Prior to this study, data regarding the incidence of PH throughout the Down syndrome lifespan, associations with comorbidities, exacerbating factors, and overall impact of PH in the Down syndrome population were lacking. Most notably, perhaps, was their finding that a vast majority (87%) of patients who suffered from recurrent PH after a previous resolution were classified as World Health Organization (WHO) Group 3 or associated with lung disease. The

study also demonstrated that obstructive sleep apnea (OSA), recurrent hypoxia, and aspiration are clear risk factors for development or recurrence of PH. Given these findings, we as providers must take an organized approach in screening for potentially preventable lung insults that contribute to the development and further progression of PH.

CLASSIFICATION AND INCIDENCE

It is well known that PH in children with Down syndrome is most frequently classified as Group 1 PH (PAH, pulmonary arterial hypertension) associated with congenital heart disease (CHD) or persistent pulmonary hypertension of the newborn (PPHN), and oftentimes a combination of the two.^{2,3} For one cohort of children with Down syndrome followed prospectively in the Netherlands, 5.2% had PPHN, which is significantly higher than the reported 0.1% in the general population.³ In the large group of children followed in the Down Syndrome Clinic at Denver Children's Hospital (n=1252), of the 28% identified as having PH, 82% had associated CHD and 45% had PPHN.² The most common cardiac congenital malformations associated with Down syndrome include atrioventricular canal, patent ductus arteriosus, atrial septal defect, and ventricular septal defect, all of which

include cardiac shunts that can lead to PH due pulmonary over circulation.^{2,3,10} The American Academy of Pediatrics (AAP) recommends an echocardiogram in the first month of life for all babies with Down syndrome; therefore, most are diagnosed and repaired in infancy.⁵

While cardiopulmonary abnormalities including CHD and PPHN are the most common etiology of PH onset in infancy, lung disease is the more common etiology seen after infancy or with recurrent disease. It appears that PH develops more readily from hypoxia in the Down syndrome population, and that children with a prior diagnosis of PH are more likely to develop a recurrence of disease in the context of a respiratory comorbidity such as OSA, intermittent hypoxia, recurrent pneumonia, and chronic aspiration. Given the high rate of respiratory comorbidities in these children, it is not surprising that 87% of children experiencing a second episode of PH after a previous resolution were classified as WHO Group 3.² For any patient with Down syndrome and PH (or history of PH), a primary pediatric pulmonologist should be identified and follow the patient along with the PH team indefinitely.

For those Down syndrome patients who have resolution of their PH, it is imperative they have regular screening for comorbid respiratory conditions despite the presence or absence of symptoms. Given what we know about this population, we are empowered to prevent the recurrence of PH in this high-risk population by continuing to regularly screen for respiratory comorbidities, rather than screening only after echocardiogram evidence of PH becomes apparent.

FREQUENT COMORBID CONDITIONS

Aspiration

A frequently overlooked cause of PH and other respiratory symptoms in Down syndrome is unrecognized aspiration. Children with Down syndrome are at significant risk for chronic aspiration due to delayed oral development, structural abnormalities, and hypotonia.¹ One study of patients with Down syndrome followed in a sleep clinic in the United Kingdom showed 16/17 computerized tomography (CT) scans done on this population revealed findings suggestive of aspiration.⁴ In the Denver cohort, 35% of all patients with Down syndrome with PH were reported to have chronic aspiration. That number increased to 48% of patients with recurrent PH, highlighting the significant role chronic aspiration can play in children with a history of PH.² The AAP recommends video fluoroscopic swallow study (VFSS) for any child with Down syndrome with "marked hypotonia, slow feeding, choking with feeds, recurrent persistent respiratory symptoms, or failure to thrive" in the first year of life. They do not provide recommendations for any routine screening.⁵ We recommend that a VFSS be performed for all children with Down syndrome, despite a presence or absence of aspiration symptoms, as part of the initial comprehensive evaluation for new PH diagnosis, recurrence of previously resolved PH, poorly controlled or worsening PH, and periodically for those with a history of diagnosed aspiration. All patients with presumed or confirmed aspiration should by regularly followed by a feeding therapist as well as a pulmonologist for ongoing assessment and monitoring.

Obstructive Sleep Apnea

There is a significant risk of OSA, found in multiple studies to be present in anywhere from 30% to 79% of all patients with Down syndrome (compared with just 2% of the general pediatric population).^{1,2} In the Denver cohort of patients with Down syndrome, 78% of those with PH were also diagnosed with OSA, showing an incredibly high association of the two diseases.² Because of the known risk factor of OSA in the Down syndrome population, the AAP recommends a sleep study by age 4 years for all children with Down syndrome, and sooner if one exhibits signs or symptoms of sleep-disordered breathing.⁵ However, as McDowell explains, relying on parental report is somewhat problematic. Parents of children with Down syndrome consistently underestimate the presence of sleep-disordered breathing. In one study, 69% of parents of children with Down syndrome denied any sleep problems, yet 54% of those same children had abnormal sleep study findings.⁶ Because of this, we recommend a standardized approach for screening for OSA in patients with history of PH or active disease, instead of determining need based on parental report.

For those children with a new diagnosis of PH (or new recurrence), a sleep study should be done as part of initial comprehensive workup, as is recommended with any child with new diagnosis of PH (not just patients with Down syndrome).⁷ For those with a history of resolved or controlled PH, we feel it is reasonable to be assessed in a sleep clinic annually so that the specialists in that clinic help determine the need for and frequency of sleep studies. And finally, in PH patients with Down syndrome who have lack of improvement or clinical worsening despite optimal PH treatment, sleep studies should be repeated every 1 to 2 years given the high rate of association of OSA and PH. Providers commonly assume that pediatric patients with Down syndrome have low adherence to prescribed respiratory support, and sometimes resist repeating sleep studies if they do not believe their patients will comply with recommendations. However, a recent study showed more than half of children (22/39)had satisfactory and regular usage of prescribed respiratory support, further emphasizing the need for ongoing OSA

screening.⁴ While adenotonsillectomy can improve sleep-disordered breathing in this population, underlying airway structure or dynamics may cause significant residual OSA. Because of this, reassessment after surgery is also imperative.¹

Parenchymal and Structural Airway Disease

Children with Down syndrome are known to have an increased incidence of pulmonary abnormalities when compared to the general population. Common airway abnormalities include anomalies such as macroglossia, tonsil and adenoid hypertrophy, laryngomalacia, tracheobronchomalacia, subglottic stenosis, and tracheal stenosis.¹ These airway abnormalities predispose patients to intermittent hypoxia, which can lead to the development of PH in this at-risk population. In one review, approximately 50% of patients with upper airway obstruction had PH documented by echocardiogram or cardiac catheterization, with 91% resolution of PH following surgery.⁸ While we know patients with Down syndrome can also have primary parenchymal lung disease (such as pulmonary hypoplasia, pulmonary lymphangiectasia, lymphoid interstitial pneumonitis, and other interstitial lung disease), they are more likely to have diffuse parenchymal disease from secondary causes such as postinfectious changes, chronic lung disease of prematurity, and chronic aspiration. Interestingly, there are significantly lower rates of asthma in the Down syndrome population, which should prompt the provider to screen for alternative causes of coughing and wheezing.¹

These well recognized comorbidities highlight the importance of proper screening for pulmonary abnormalities, including advanced imaging with high-resolution chest CT at the time of PH diagnosis or recurrence, and need for good, ongoing pulmonary specialty care. Furthermore, it is has been shown that patients with Down syndrome may not respond to pulmonary vasodilators in the same way as patients without Down syndrome, potentially indicating that ongoing pulmonary (or other) insults have not been properly identified or treated correctly prior to initiation of PH-specific Table 1. Seattle Children's Hospital screening guidelines for children with Down syndrome and PH or at risk of developing PH

	AAP standard of care for all patients with Down syndrome	Any child with chronic respiratory conditions	New PH diagnosis or recurrent episode	PH resolved or well controlled	No improvement in PH / worsening
Echocardiogram	First month of life	Consider screening for PH every year	With initial evaluation	Annually until school age for resolved PH (CHD, PPHN, or other cause PH) At least annually indefinitely for well- controlled PH	As frequent as PH team suggests
Pulmonology consult	N/A	Evaluation by pediatric expert and continue to follow regularly	With initial evaluation if not previously established	Continue to follow regularly until lung disease r/o as contributing factor	Continue to follow regularly until lung disease r/o as contributing factor
VFSS	In first year of life only if symptoms present	As soon as respiratory symptoms become apparent	With initial evaluation	Annual evaluation by speech therapist and VFSS until age 6 years; consider annual screening thereafter for those with history of diagnosed aspiration	At least annually (more frequent if unexplained worsening)
Sleep study	By age 4 years	Per primary pulmonologist	With initial evaluation	Consider annual sleep clinic evaluation	Annually repeat after any surgical airway management
Chest CT	N/A	Should be strongly considered	With initial evaluation	N/A	Consider repeating at intervals decided with primary pulmonologist to screen for ongoing evidence of aspiration, other parenchymal disease, or pulmonary venous obstruction
Lab surveillance: BNP, Thyroid, ANA	Thyroid: NB, 6 months, 12 months, annually	Consider BNP with echo screening	With initial evaluation	At least annually	At least annually. BNP more frequently to trend response to treatment

therapy.⁹ The Pediatric PH Guidelines from the American Heart Association and American Thoracic Society also highlight the importance of identifying and treating primary or secondary respiratory disease prior to the initiation of long-term pulmonary vasodilator therapy.⁷

CONCLUSION

Given what we currently know about Down syndrome and PH, our PH center at Seattle Children's Hospital has developed guidelines and standards of care for the patient with Down syndrome throughout their lifespan (Table 1). Both inpatient and outpatient PH referrals too often come after months to years of unrecognized pulmonary insults. With proper education and reinforcement of proposed guidelines for screening, our hope is that comorbidities are recognized and treated prior to the development of or worsening of PH, ideally prior to referral to the PH center, but certainly as part of the ongoing, comprehensive care of the child with Down syndrome and PH.

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