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Decreased mortality of pulmonary arterial hypertension in Duchenne muscular dystrophy and Down syndrome

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Abstract

The Pulmonary Hypertension Association summarized the Advanced therapies initiated with confirmation through Key to treating individuals with DMD or DS is the 52 NCBI.  Many disorders of the body cause APAH.  Two genetic conditions having co-occurrence with APAH are

Introduction

The 5th World Symposium on Pulmonary Hypertension, held in Nice, France, February 27 to March 1, 2013, identifies four specific types of PAH: Idiopathic, Familial, Drug or Toxic Induced and Associated. Idiopathic PAH (IPAH) causes are unknown (Saji, 2014). Familial PAH (FPAP) has a genetic cause (Chew, 2011). Drug-induced PAH is a growing concern (Peacock, Murphy, McMurray, Baballero & Stewart, 2007). The most common type of PAH, associated (APAH), occurs along with other medical conditions (Chew et al., 2017). Recent studies have provided insight in the diagnosis and screening for both familial and associated pulmonary arterial hypertension. Research has led to earlier diagnosis of and screening for PAH (Tonelli et al., 2013).

Statement of the Problem

Identifying the specific underlying pathophysiology and etiology of PAH when associated with DMD and DS is vitally important to treatment. It is also important to understand that options with proven, evidence-based modalities particular to co-morbid conditions can have positive influence on patient outcomes. From increased life expectancy to improved quality of life. Reviewing research which has been completed helps deepen the understanding of the direction future investigation in PAH is taking.

Research Questions

> What is the correlation between genetic disorders like DMD and DS with increased incidence of PAH?
> What has current and existing research shown in the understanding of pulmonary arterial hypertension?
> What is the recommended, evidence based treatment modality for PAH specific to DMD and DS?
> Among individuals with Duchenne muscular dystrophy and DMD syndrome with co-morbid pulmonary arterial hypertension (PAH), has early recognition and treatment led to statistically significant increase in life expectancy versus previously undiagnosed or unrecognized PAH?

Literature Review

Correlation between DMD or DS and incidence of PAH

DMD progresses with muscle wasting and connective tissue disorders. These processes result in eventual dysplasia of the diaphragm and mediastinal adipose body containing thirty-one individuals with DMD and eleven healthy individuals has shown a significant correlation (r = 0.39, p = 0.0391) between plasma nitric oxide levels and ejection fraction measured by echocardiogram in the DMD group (Kasai et al., 2004). The finding suggests that there is a significant decrease in production of nitric oxide as part of the disease process of DMD. Decreased levels of nitric oxide have a direct effect on prostacyclin and a converse effect on endothelin. A study of eight individuals with advanced development of DMD were evaluated by right heart catheterization. A mPAP of > 40 mmHg (Yotsukura, Miyagawa, Tsuchiya, Ishihara & Ishikawa, 1998).

The majority of CHD in DMD syndrome are related to septal wall and atrioventricular valve defects (Li et al., 2012). From May of 2007 to December of 2006, 743 patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. Logistic regression analysis revealed that anatomic septal systolic blood pressure, VSD, PDA and combined lesions were independent risk factors of PAH in CHD (Li et al., 2014).

Literature Review Continued

Current Understanding of PAH

> The Pulmonary Hypertension Association summarized the pathophysiologic pathways of PAH at its 2017 symposium:
> Nitric oxide (NO): An endogenous pulmonary vasodilator, also possesses anti-proliferative properties. A relative deficiency of endothelial NO in the pulmonary vasculature may be one mechanism which contributes to the development of PAH.
> Endogenous prostacyclins: Systemic and pulmonary vasodilators, anti-proliferative agents that also have antithrombotic/antiplatelet effects. Relative deficiency or down-regulation of endogenous prostacyclin may contribute to the development of PAH.
> Endothelin-1: An endogenous vasoconstrictor. Up-regulation of endogenous endothelin-1 may also contribute to the pathogenesis of PAH.
> The small vessel arteriopathy in PAH leads to a progressive rise in RV afterload and pulmonary vascular resistance (PVR). As a result, the RV undergoes remodeling changes, including right ventricular hypertrophy, dilation and finally dysfunction. If PAH is left untreated, right ventricular failure will ultimately result in patients experiencing syncope, angina, edema and abdominal distention (Favilli et al., 2015). Right ventricular failure is the most common cause of death in patients with PAH (Sibbitt and Morrell, 2012).

BPMP22 epistatic effect on KCNQ3 and TGF-Beta resulting in smooth muscle potassium and calcium channelopathy (Ma et al., 2013).

PDLIM5 is produced in the smooth muscle cells of the pulmonary artery (Zhou, Chen and Raj, 2015). Within the past year the American Lung Association has begun investigating the effect hypoxia has on the PDLIM5 expression. Of particular note is the suppressive effect PDLIM5 plays on the activation of a downstream protein SMAD2/3, which is responsible for cell signaling in smooth muscle (Ousterout et al., 2015). This study is scheduled to conclude in 2019.

Discussion

Although there has been significant research in regard to DMD, PAH and DS individually, limited study has occurred on the correlation between either the special populations and PAH. Furthermore, it would seem that there are no reported studies on the pulmonary arterial hypertension (PAH) in PAH, regardless of co-morbid conditions, is the profound take away. Evidence-based treatment algorithms are available for PAH, centered around the functional classification of the patient.

Applicability to Clinical Practice

> Supportive therapy and general measures with expert referral upon suspicion.
> Advanced therapies initiated with confirmation through targeted drugs and vasoactivity testing.
> Treatment is centered around the individual's limitation of physical activity.
> In individuals the mechanism of a vasoreactive response are treated with calcium channel blockers.
> Immunos that do not demonstrate a vasoreactive response:
> - PH with slight limitation - Ambisentan & tadalafil
> - PH with marked limitation - Ambisentan & tadalafil
> - No improvement or deterioration- double or triple therapy
> Key to treating individuals with DMD or DS is the recognition of changes in behavior and activity by the provider

References

Sibbitt, W.L., et al. (2012). Genetic, Pathogenic Modifying to Congenital Heart Disease in the Saturated Donor Genome. Circulation. doi:10.1161/CIRCULATIONAHA.111.078672
Tonelli, A., et al. (2013). The Role of Early Intervention and Treatment pertaining to individuals with DMD or DS. The connection of the pathophysiology of the pulmonary arterial hypertension (PAH) involved in PAH, regardless of co-morbid conditions, is the profound take away. Evidence-based treatment algorithms are available for PAH, centered around the functional classification of the patient.

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