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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 fact that pulmonary hypertension (PH) is a serious and life-threatening condition. The small vessel arteriopathy in PH leads to a progressive decrease in physical ability and communication capacity. Genetic research has allowed for earlier identification of, or predisposition for, the development of PH. Work has also progressed toward manipulation of the genetic level to decrease the severity and even eradicate the cardiopulmonary disorder. This information is beginning to be applied in treatment for individuals with PH. A literature review was conducted to identify the research, prediction methods and treatment of PH in individuals with Duchenne muscular dystrophy (DMD) and Down syndrome (DS) individually. There was evidence of research focusing on PH as it pertains particularly to DMD and DS.

Introduction

The 5th World Symposium on Pulmonary Hypertension, held in Nice, France, February 27 to March 1, 2013, identified four specific types of PH: Idiopathic, Familial, Drug or Toxin Induced and Associated. Idiopathic PH (IPAH) causes are unknown (Saji, 2014). Familial PH (FPAP) has a genetic cause (Chew, Loyd & Austin, 2006). Down syndrome (DS) is a genetic disorder that is caused by an extra chromosome 21 (Kasai et al., 2004). The most common type of PH, 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 PH (Tonelli, et al., 2013). Unfortunately, co-morbid and/or exacerbating conditions often dictate patient outcome (Tonelli, et al., 2013). Many disorders of the body cause APAH. Two genetic conditions having co-morbid occurrence of APAH are Down syndrome and Duchenne muscular dystrophy. Both of these disorders have high mortality rates.

Statement of the Problem

Identifying the specific underlying pathophysiology and etiology of PH 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. Researching work that has been completed helps deepen the understanding of the direction future investigation in PH 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 Down 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

MDPD progresses with muscle wasting and connective tissue disorders. These processes result in eventual dysplasia of the diaphragm and PMG remodels. The body containing thirty-one individuals with DMD and eleven healthy individuals has shown a significant correlation (r = 0.38, p = 0.0391) between production of nitric oxide 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 > 20 mmHg was noted in all subjects, while five of the eight had a mean pulmonary arterial pressure of > 40 mmHg (Yotsukura, M., Miyagawa, M., Tsuya, T., Ishihara, T., and Ishikawa, K. (1988). A study evaluating the effect hypoxia has on the PDLIM5 protein 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 PDLIM 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 (Ousterut, et al., 2015). This study is scheduled to conclude in 2019.

Discussion

Although there has been significant research in regard to DMD, PH and DS individually, limited study has occurred on the correlation between either the specific populations and PH. Furthermore, it would seem that there are no reported studies on the correlation or quality of life related to early intervention and treatment pertaining to individuals with DMD or DS. The correlation of the pathophysiologic processes 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.

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-platelet 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, dilatation 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).

Applicability to Clinical Practice

- Supportive therapy and general measures with expert referral upon suspicion.
- Advanced therapies initiated with confirmation through acute vasoreactivity testing.
- Treatment is centered around the individual’s limitation of physical activity.
- Individualized medications treated a vasoreactive response are treated with calcium channel blockers.
- Immunos that do not demonstrate a vasoreactive response:
  - PH with slight limitation- Ambientras & tadalafil
  - PH with marked limitation- Ambientras & thalidomide
- 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


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