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Decreased Mortality of Pulmonary Arterial Hypertension in Duchenne Muscular Dystrophy and Down Syndrome

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Abstract

The genetic cause of significant disorders like Down syndrome (DS) and Duchenne muscular dystrophy (DMD) is well documented. Pulmonary arterial hypertension (PAH), a co-morbid condition, is tied to mortality among these groups. Individuals with the ability to communicate their symptoms and actively participate in treatment are at an advantage with subsequent benefit. DS and DMD significantly decrease physical ability and communication capacity. Genetic research has allowed for earlier identification of, or predisposition for, the development of PAH. 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 to treatment for individuals with PAH. A literature review was conducted to identify the research, prediction methods and treatment of PAH in individuals with Duchenne muscular dystrophy (DMD) and Down syndrome (DS) as well as comprehend morbidity or increased life expectancy among those groups. The results showed significant gains in the understanding of PAH, DS and DMD individually. There was little evidence of research focusing on PAH in DS as it pertains particularly to DS or DMD.

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 Toxin Induced and Associated. Idiopathic PAH (IPAH) causes are unknown (Saji, 2014). Familial PAH (FPAH) has a genetic cause (Chew, Loyd & Austin, 2017). Drug or Toxin induced PAH is a growing concern (Peacock, Murphy, McMurray, Babaliero & 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).

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 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 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

MDP progresses with muscle wasting and connective tissue disorders. These processes result in eventual dysfunction of the diaphragm and associated muscles. Body composition including thirty-one individuals with DMD and eleven healthy individuals has shown a significant correlation (r = -0.39, p = 0.0981) between PAH levels, systolic blood pressure, VSD, PDA and combined lesions (Li et al., 2012). From May of 2007 to December of 2008, 704 all subjects, while five of the eight had a mean pulmonary arterial pressure of > 40 mmHg, 75% with Duchenne muscular dystrophy (MDP) 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. MDP, patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. Logistic regression analysis revealed that all of the systemic artery systolic blood pressure, VSD, PDA and combined lesions were independent risk factors of PAH in CHD (Li et al., 2014).

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 pathogenesis which contributes to the development of PAH.
- Endogenous prostacyclin: Systemic and pulmonary vasodilators, anti-proliferative agents that also have anti-thrombotic/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).

Literature Review Continued

Supportive therapy and general measures with expert referral upon suspicion.
- Advanced therapies initiated with confirmation through cathlab evaluation and vasoactivity testing.
- Treatment is centered around the individual's limitation of physical activity.
- Individuals may be administered a vasoactive response are treated with calcium channel blockers.
- Immunos that do not demonstrate a vasoactive response:
  - PH with slight limitation - Ambienstar & tadalafil
  - PH with marked limitation - Ambienstar & 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


Applicability to Clinical Practice

- Supportive therapy and general measures with expert referral upon suspicion.
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Discussions

Although there has been significant research in regard to DMD, DS and individuals with special conditions, limited study has occurred on the correlation between either the special populations and PAH. Furthermore, it would seem that there are not enough studies on the correlation between the quality of life related to early intervention and treatment pertaining to individuals with DMD or DS. The correlation of the pathophysiologic changes involving 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.