2018

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 Duchenne syndrome (DS) and Down syndrome (DS) 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 at 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 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 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, identified four specific types of PAH: Idiopathic, Familiar, Drug or Toxin Induced and Associated. Idiopathic PAH (IPAH) causes are unknown (Saji, 2014). Familiar PAH (FP AH) has a genetic cause (Chew, Loyd & Austin, 2014). Drug-induced PAH is growing concern (Peacock, Murphy, Mitchell, Volin & Peacock, 2008). Both of these disorders have high mortality rates. Down syndrome and Duchenne muscular dystrophy.

Many disorders of the body cause APAH. Two genetic types, have high mortality rates.

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 dysfunction of the diaphragm of DMD muscular dystrophy causing body comparing thirty-one individuals with DMD and eleven healthy individuals has shown a significant correlation ($r = -0.391$, $p = 0.0391$) 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 > 20 mmHg was noted in all subjects, while five of the eight had a mean pulmonary arterial pressure of > 40 mmHg (Matsukura, Miyagawa, Tsuya, Ishihara & Ishikawa, 1998).

The majority of CHD in Down syndrome are related to septal wall and atrioventricular valve defects (Li et al., 2012). From May 2007 to December of 2008, 724 patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. Logistic regression analysis revealed that an acute 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 pathophysiological 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 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 distension (Favilli et al., 2015). Right ventricular failure is the most common cause of death in patients with PAH (Sitbon and Morrell, 2012).

SMPI22 epistatic effect on KCNQ3 and TGF-Beta result in smooth muscle potassium and calcium channelopathy (Ma et al., 2013).

PDL1MS protein is produced in the smooth muscle cells of the pulmonary artery (Chen, Ren and Raj, 2015). Within the past year, the American Lung Association has begun investigating the hypothesis on the PDLMS expression. Of particular note is the suppressive effect of PDLMS play an activation of a downstream protein SMA/23, 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, DS and PAH 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 life expectancy or mortality among those groups. The literature review was conducted to identify the research, prediction methods and treatment of PAH in individuals with DMD and DS (or DS) as it pertains particularly to DMD or DS.

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 this 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 Continued

Applicability to Clinical Practice
- Supportive therapy and general measures with expert referral upon suspicion.
- Advanced therapies initiated with confirmation through specialized laboratories and vascuroscopy testing.
- Treatment is centered around the individual's limitation of physical activity.
- In individuals with moderate to severe pulmonary hypertension, a vasoreactive response are treated with calcium channel blockers.
- Immunosuppressants 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